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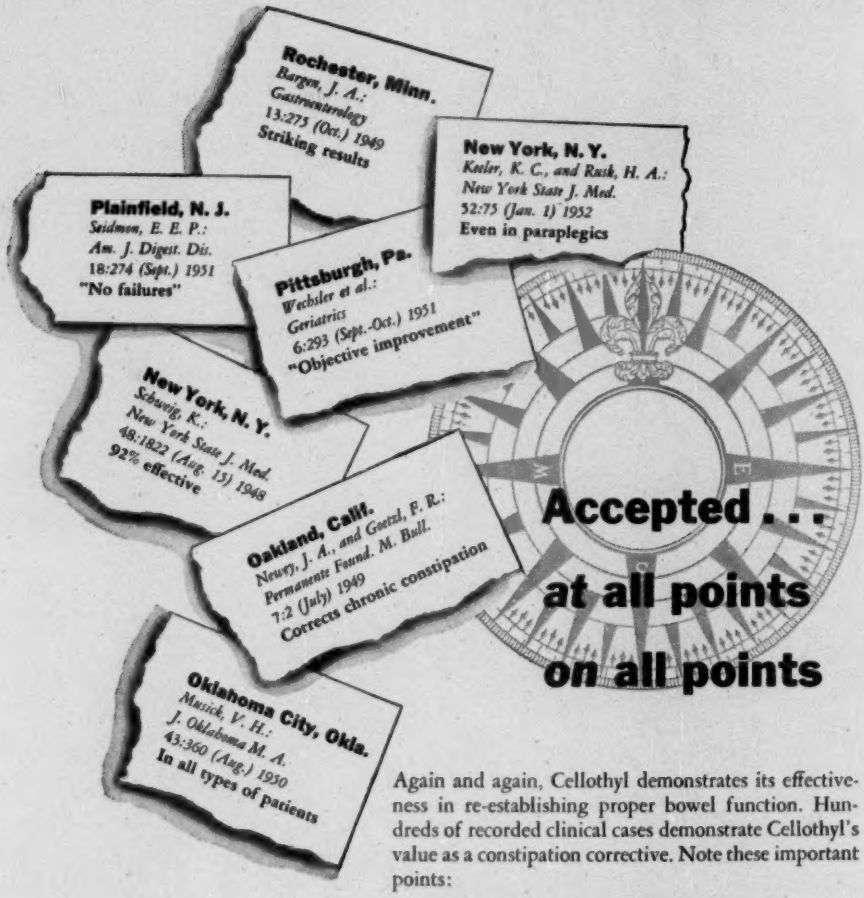

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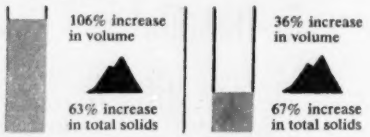

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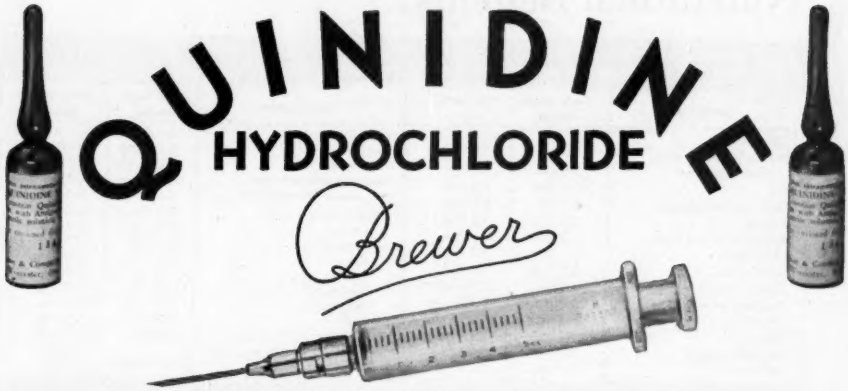

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3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1: 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1: 939 (April Part II) 1950

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1. Underwood, J. C., and Rockland, L. B.: Food Research, in press.
2. Miner Laboratories, Chicago, Illinois. (1952)
3. Davis, W. B.: Determination of Flavanones in Citrus Fruits, Anal. Chem. 19:476 (July) 1947.
4. Underwood, J. C., and Rockland, L. B.: Arch. Biochem., in press. All others from figures taken from the literature and data compiled by Research Department, Sunkist Growers. From known tissue distribution figures, appropriate adjustments have been made to reflect the composition of the entire edible portion in those cases where the original data referred to screened juice.

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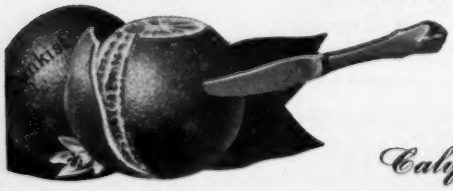

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VOLUME 90 DECEMBER 1952 NUMBER 6

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Editorials

HAZARDS OF ANTIBIOTIC THERAPY

THE ASTONISHING dislocation of the normal bacterial flora of the upper air passages and gastrointestinal tract following antibiotic administration was discussed in this column last year.[1] Among the vast amount of data demonstrating the possible deleterious effects of these changes, a report in the present issue of the ARCHIVES is of particular importance. Barach, Bickerman, and Beck report that among 81 patients with long-standing bronchitis and bronchiectasis who were treated with the broad-spectrum antibiotics there was a significant increase in micro-organisms not sensitive to these antibiotics—namely, Proteus vulgaris, Pseudomonas aeruginosa, Cryptococcus, Aspergillus, Micrococcus pyogenes var. aureus, Klebsiella pneumoniae, and Candida albicans. In seven patients of their series death occurred apparently from an extensive pulmonary infection or septicemia due to one of these micro-organisms during therapy with aureomycin, terramycin, or chloramphenicol. Four deaths were attributed to Proteus vulgaris infections and one death each to infection with Cryptococcus, Aspergillus and Ps. aeruginosa. The case histories reveal that the fatalities occurred in patients with long-standing and debilitating disease, after prolonged therapy. In the case in which Aspergillus of the lung was cited (Case 10) as the final cause of death, a depressant effect of chloramphenicol on the bone marrow may have been a contributing cause. These authors feel that in long-standing pulmonary infections due to a mixed bacterial flora prolonged use of penicillin by either inhalation or parenteral administration is relatively safe but that continued use of the broad-spectrum antibiotics for periods longer than five or six days is fraught with considerable risk. In view of the results cited here, their caution appears justified.

A recent report by Yow [2] also emphasized the remarkable increase in B. proteus and Ps. aeruginosa infections accompanying the use of antibiotics which suppress other strains. In this series there were three deaths, two due to P. vulgaris septicemia and one to Ps. aeruginosa empyema. He found that a combination of streptomycin with sulfonamides constituted the most effective therapy against Proteus infections and polymyxin B was most effective against Ps. aeruginosa, but no antibiotic or chemotherapeutic agent or combination of antibacterial agents now in wide clinical use is capable of suppressing the growth of these two micro-organisms consistently.

1. Bloomfield, A. L.: Effect of Antibiotics on Bacteria of the Upper Air Passages, editorial, A. M. A. Arch. Int. Med. **88**:135 (Aug.) 1951.

2. Yow, E. M.: Development of Proteus and Pseudomonas Infection During Antibiotic Therapy, J. A. M. A. **149**:1184 (July 26) 1952.

Miller and Bohnhoff [3] in 1946 showed that in the case of meningococci if therapy with streptomycin was insufficient quantitatively quickly to suppress growth, acquired resistance to the antibiotic occurred and eventually a stage was reached in which the micro-organisms came to depend on streptomycin for subsistence. Others have made similar observations. Garrod,[4] for example, found that with certain strains of staphylococci and Ps. aeruginosa grown in the presence of penicillin the antibiotic not only failed to prevent rapid multiplication but actually stimulated growth, as demonstrated by comparison with cultures on the same media which did not contain penicillin. Pappenfort and Schnall [5] observed the development of moniliasis in a significant number of patients treated with aureomycin. They then set up in vitro experiments in which it was demonstrated that aureomycin added to culture media stimulated the growth of Candida albicans, Cryptococcus neoformans and Saccharomyces cerevisiae.

While the deaths in the series of Barach and co-workers and of Yow were in severely debilitated patients with advanced chronic disease in the respiratory or urinary tracts, there seems little doubt that therapy with broad-spectrum antibiotics incapable of suppressing the micro-organisms eventually responsible for death may actually have contributed to the final result by creating conditions in which their growth proceeded unimpaired. The lesson to be learned seems clear. Before the therapeutic attack with antibacterial agents is begun, a knowledge of the total bacterial flora of the area being treated is highly desirable. If possible, the in-vitro susceptibility of the micro-organisms one wishes to eliminate should be determined. Unless the patient is known to be sensitive to the antibiotic or chemotherapeutic agent indicated by these tests to be most effective, the drug should be administered in full dosage, but in the case of the broad-spectrum antibiotics usually not for longer than a week at a time. Recultures should be made at intervals of a few days to detect the ascendency of other harmful strains in the area being treated, so that the attack may be shifted if need be. More study is needed in the discovery of effective combination therapy to be used in mixed infections, so that the total bacterial flora may be attacked, and there is urgent need for a safe antibiotic which will be effective against a wide range of yeasts and fungi.

Another very real hazard in antibiotic therapy is pointed out in the timely paper of Bateman, Barberio, Grice, Klopp, and Pierpont (p. 763) in the present issue of the ARCHIVES. These investigators, in a clinical study prompted by the suggestion that large doses of antibiotic might suppress tumor growth, gave extremely large doses of terramycin and penicillin to a series of far-advanced cancer patients. The dosages of terramycin averaged 2 to 4 gm. daily and those of penicillin were 12,000,000 units at intervals of about four hours. In 8 of their 10 cases in which terramycin was administered parenterally there was rapidly progressive azotemia followed by death. In two of the three patients receiving penicillin in the dosage mentioned sudden death occurred after the third and fourth injections respectively.

3. Miller, C. P., and Bohnhoff, M.: Streptomycin Resistance of Gonococci and Meningococci, J. A. M. A. **130**:485 (Feb. 23) 1946.

4. Garrod, L. P.: Reactions of Bacteria to Chemotherapeutic Agents, Brit. M. J. **1**:205 (Feb. 3) 1951.

5. Pappenfort, R. B., Jr., and Schnall, E. S.: Moniliasis in Patients Treated with Aureomycin, A. M. A. Arch. Int. Med. **88**:729 (Dec.) 1951.

In the third patient convulsions developed, but recovery followed. Experimental evidence is adduced to support the clinical impression that when the ability of the kidney to excrete these agents rapidly is exceeded extremely toxic effects occur.

While it is only very rarely that these two antibiotics, which up to now have not been suspected of serious nephrotoxic effects, are used in doses even close to those employed in the cases cited, it is important that the upper limits of tolerance for them be established. There is a tendency to use larger and larger doses of penicillin in such diseases as subacute bacterial endocarditis, and since the possible harmful effects of aureomycin intravenously have been pointed out [6] terramycin is being used more frequently and in larger doses intravenously. Again, the need for caution in the use of antibiotics which up to now have not been regarded as potentially dangerous from the standpoint of producing azotemia seems obvious.

PAUL S. RHOADS, M.D.

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6. Lepper, M. H.; Wolfe, C. K.; Zimmerman, H. J.; Caldwell, E. R., Jr.; Spies, H. W., and Dowling, H. L.: Effect of Large Doses of Aureomycin on Human Liver, A. M. A. Arch. Int. Med. **88**:271 (Sept.) 1951. Lepper, M. H.; Zimmerman, J. H.; Carroll, G.; Caldwell, E. R., Jr.; Spies, H. W.; Wolfe, C. K., and Dowling, H. F.: Effect of Large Doses of Aureomycin, Terramycin, and Chloramphenicol on Livers of Mice and Dogs, ibid. **88**:285 (Sept.) 1951.

EVALUATION OF 1-HYDRAZINOPHTHALAZINE ("APRESOLINE") IN TREATMENT OF HYPERTENSIVE DISEASE

R. D. TAYLOR, M.D.
HARRIET P. DUSTAN, M.D.
A. C. CORCORAN, M.D.
AND
IRVINE H. PAGE, M.D.
CLEVELAND

DEMONSTRATION of a humorally mediated pressor mechanism of central-nervous origin [1] prompted the suggestion that this system might sometimes participate in the genesis of essential hypertension. Since the pressor effect was suppressed by "apresoline" (1-hydrazinophthalazine, Ciba), it was considered possible that patients in whom the mechanism was operative would respond favorably and relatively specifically to treatment with this drug. It was recognized that the drug has properties which might tend to decrease arterial pressure by other means than inhibition of cerebral pressor activity.

With these considerations in mind, a survey was initiated of the therapeutic effects of "apresoline" when administered as the sole antipressor agent to patients suffering from a wide spectrum of hypertensive disease.

METHOD OF STUDY

Ninety-seven patients were treated with "apresoline" for at least 3 months and usually for 12 months or more. Of these, 58 were hospitalized for close observation and at least preliminary treatment; as a group these were more severely ill than the 39 outpatients. Blood pressures were measured twice daily by nurses in the hospital or by the patient or a relative at home.

"Apresoline" was not given until the graphically recorded averages of these pressures had been constant for two or more weeks, during some or all of which time placebos were usually prescribed. The complications of hypertensive disease (evidences of heart failure, azotemia, urinary tract infection) were relieved by appropriate measures during the control period, and this treatment was continued while "apresoline" was given.

In the clinical survey, special attention was paid to the presence of familial hypertension and to evidences of diseases of the urinary tract and toxemia of preg-

From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute.

1. Taylor, R. D.; Page, I. H., and Corcoran, A. C.: A Hormonal Neurogenic Vasopressor Mechanism, A. M. A. Arch. Int. Med. **88**:1, 1951.

nancy. In addition to complete physical examination, the optic fundi and heart were reexamined at least weekly in the hospital patients and monthly in outpatients. Retinal changes were graded 1 to 4+ as previously described.[2]

Blood cell counts and blood hemoglobin determinations were repeated at intervals. Electrocardiograms and teleoroentgenograms were made at the outset and at intervals during the study. Cardiac enlargement was measured from the latter by the tables of Ungerleider and Clark.[3]

Addis measurements of maximum urinary concentrating power, proteinuria, and sediment were repeated at monthly or bimonthly intervals for nearly all patients, as were measurements of urea clearance. The appraisal of renal function in inpatients included estimates of glomerular filtration rate and effective renal plasma flow from plasma clearances of mannitol and *p*-aminohippurate.

Classification.—For convenience in the evaluation of responses to treatment, the patients were separated into classes of hypertensive disease. These sometimes overlapped. They are as follows. Early essential: a state of persistent diastolic hypertension, with moderate subjective symptoms but without evidence of advancing vascular disease. Most patients had familial hypertension. Severe essential: a progression of the early essential state with retinal, cerebrovascular, cardiac, and/or renal evidences of advancing hypertensive vascular disease and associated disability. Malignant: a syndrome characterized by papilledema, retinal hemorrhages and exudates, objective evidences of hypertensive heart disease, and proteinuria and hematuria, usually associated with impaired renal function and commonly accompanied by weight loss. Renal: a clear-cut history of toxemia of pregnancy, polycystic kidney, pyelonephritis, and so on, without familial hypertension. Diencephalic: a syndrome characterized by episodic blotchy-red blush over the neck and upper thorax, associated with hyperhidrosis, hyperperistalsis, and crying spells.[4] Ancestral:[5] hypertension in descendants of Mediterranean national groups who tend to volatile and facile responses to situational stimuli and vigorous expressions of their feelings. Frequently associated were evidences of gastrointestinal autonomic instability. The symptoms, except for the absence of flush, resembled those of the diencephalic class. Hypertensive disease in sympathectomized patients: 11 of these patients had had a bilateral lumbodorsal sympathectomy and 1 celiac ganglionectomy and splanchnicectomy.

The scope of data collected during this study made it desirable for us to devise a severity index which would numerically summarize the relative status of the patients' disease. This was done as follows:

A composite severity index was assembled from four panels, namely, blood pressure and the status of cardiac, renal, and cerebral functions, each graded 1 to 4 (Table 1). The blood-pressure grading was from increments of averages of diastolic arterial pressure. Grading of the other panels was done by assigning values ranging from 0.2 to 0.8 to each of five positive findings. Under the cardiac panel these were American Heart Association functional classifica-

2. Page, I. H, and Corcoran, A. C.: Arterial Hypertension, Ed. 2, Chicago, Year Book Publishers, Inc., 1950.

3. Ungerleider, H., and Clark, C. P.: A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on Teleoroentgenogram, Am. Heart J. **17**:92, 1939.

4. Page, I. H.: A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, Am. J. M. Sc. **190**:9, 1935.

5. Taylor, R. D., and Page, I. H., in Current Treatment of Medical Diseases, edited by A. Smith, New York, Paul B. Hoeber, Inc., to be published.

tion, intensity of apical thrust or change in rhythm, grade and character of murmurs, degree of enlargement, and estimates of electrocardiographic abnormality. Under the renal category, the factors were proteinuria, hematuria, concentrating power (Addis test) and effective renal blood flow and glomerular filtration rate. Among outpatients, filtration rate was estimated as urea clearance in percentage of normal times 1.2 and a corresponding rating arbitrarily assigned to renal blood flow. The grading of cerebral status was from examination of the optic fundi and the presence of subjective or objective evidences of cerebrovascular disease; the arteriolar changes were the sum of estimates of constriction and sclerosis, each graded 1 to 4+ divided by 2; the retinal changes considered were the sum of estimates of degree of hemorrhage and exudate divided by 2; disks were considered only as to the presence or absence of papilledema. Subjective evidence (headache, dizziness, encephalopathy, paresthesia) and objective evidence (sensory, motor, psychic losses) of cerebrovascular disease were graded from their severity as

TABLE 1.—*Composition of Severity Index* *

Panel	0	1	2	3	4
Average of diastolic pressures mm. Hg	95	96-110	111-125	126-140	140
CARDIAC:					
AHA functional class	0	I	II	III	IV
Physical examination:					
Thrust or rhythm	Normal	Thrust 1+	Thrust 2+	Thrust 3+	Gallop or fibrillation
Murmurs	0	Systolic Gr. 1	Systolic Gr. 2	Systolic Gr. 3	Systolic Gr. 4 or aortic diastolic
Enlargement, %	0	10	11-20	21-30	30
ECG estimate	Normal	"No diagnostic change"	"Myocardial change"	Strain	Conduction defects: abnormal rhythms
RENAL:					
Proteinuria, gm./24 hr.	0.1	0.11-0.2	0.21-1.0	1.1-3.0	3.0
Hematuria, ml./12 hr.	0.5	0.51-1.0	1.1-2.0	2.1-5	5.0
Maximum specific gravity	1.028	1.027-1.025	1.024-1.021	1.020-1.017	1.017
RBF cc. per 1.7 sq. m./min.	1000	999-750	749-500	499-250	250
GFR cc. per 1.7 sq. m./min.	120	119-110	109-80	89-40	40
CEREBRAL:					
Fundi: Arterioles	0	1+	2+	3+	4+
Retinae	0	0 (0.2)	0 (0.4)	1+-2+	2+
Disks	0	0 (0.2)	0 (0.4)	0 (0.6)	Papilledema
Subjective signs	0	1+	2+	3+	4+
Objective signs	0	0 (0.2)	0 (0.4)	1+	2+

* For an explanation of the severity index and the various panels, see text.

1 to 4+. Values indicated by numerals in brackets were assigned to retinae and disks even in the absence of positive findings, these being determined by the estimates of arteriolar change, as were also the values indicated in Grades 1 and 2 of the objective-sign category. These seemingly arbitrary values are justified by the fact that cerebrovascular lesions are usually demonstrable at autopsy in patients who have shown during their lifetime only changes in the retinal arterioles.

Thus the index (Table 1) is one in which the most desperately ill score 16, with 4 points each for degrees of arterial hypertension and the estimates of cardiac, renal, and cerebrovascular disease. These estimates are based on the summation of five findings under each panel other than arterial pressure. A single minimally-positive finding adds 0.2 and a maximally-positive finding 0.8. To illustrate the method and also to present representative results in a less condensed manner, case histories and graphic records of eight patients are appended.

Responses to "apresoline" were grouped according to changes in average diastolic pressure. By groups, Group I are patients who achieved a persistently normal diastolic pressure; in Group II this pressure reached levels persistently less than 110 and often less than 100 mg. Hg; in Group III the level during treatment was consistently less than 120 mm. Hg, sometimes reaching 110; pressures in Group IV were not affected by treatment.

Method of Administration.—Since this study was based on the concept that the drug might sometimes have a virtually specific effect, the effort was made to secure a thorough clinical trial in every patient. There is no means at hand of selecting in advance patients who will respond favorably; consequently, every patient was given the drug in maximal tolerated or effective dosage over an adequate test period. Since some very favorable responses did not appear until the drug had been taken for four to five weeks, treatment was continued for at least eight weeks without benefit before the test was considered a therapeutic failure. Side-effects and toxic symptoms are reviewed hereafter; although frequent, they were rarely uncontrollable and usually remitted as treatment continued. Patients were, therefore, forewarned of the likelihood of unpleasant sensations, as a part of the program of enlisting their full cooperation. Omission of this step sometimes resulted in failure of the whole effort.

After many trials, the drug was found to be more effective and best tolerated when taken four times daily, after meals and at bedtime. The dose at the outset was 25 mg. four times a day; this was increased after two to three days of uneventful treatment to 50 mg. four times a day and thereafter by increments of 50 mg. per dose every two to four days to a maximum of 800 mg. daily or until blood pressure decreased. As much as 5 gm. has been given in the course of a day, but with no more benefit than from 800 mg. and with more toxic effects. After pressure had reached a "floor," dosage was reduced to the least amount found to maintain a maximum therapeutic effect; this was sometimes as little as 50 mg. four times a day. When placebos were substituted the blood pressure began to rise toward previous hypertensive levels in two to four days. When administration of "apresoline" was resumed after its discontinuance, the same cautious increments of dosage and regard for side-effects were necessary as at the initiation of treatment.

RESULTS

Blood Pressure (Table 2).—Possibly because of the greater average severity of hypertensive disease in the hospitalized patients, their incidence of favorable response was less than that of the outpatients. Thus, 10 (17%) of the 58 fell into Group I in response and 18 (31%) into Group II, while among outpatients 14 (36%) were in Group I and 15 (38%) in Group II. Although Group III and IV responses were considered therapeutic failures, some patients in Group III showed objective and subjective improvement. The systolic pressures of some patients in Groups I and II ranged often from 150 to 180 mm. Hg and were notably labile, rising sometimes to 200 mm. Hg (Cases 1 and 6) under relatively minor stress. Placebos were substituted for the drug in the case of six inpatients and eight outpatients some weeks or months after attainment of a favorable response; in all, pressure resumed previous hypertensive levels within two to seven days and returned to its former therapeutic level when the drug was resumed.

Classification and Response (Table 3).—In general, those patients in whom psychogenic or neurogenic mechanisms might be presumed to predominate responded most favorably. Thus, Response Groups I and II included 9 of 15 patients classed as having early essential hypertension, 6 of 8 classed as having diencephalic hypertension, and 15 of 19 classed as having the ancestral form. In contrast, only two of nine with renal hypertension showed good results. Patients with severe essential and malignant hypertension stood midway between these classes, 18 of 35 and 17 of 29, respectively, being in Groups I and II. It has been stated that

TABLE 2.—*Responses to "Apresoline": Distribution of Response Groups as to Age, Diastolic Pressures, and Severity Index*

Response Groups	No.	%	Age	Rating of Diastolic Pressure		Rating of Severity Index	
				Pre-treatment	Post-Treatment	Pre-treatment	Post-Treatment
Hospital patients							
I	10	17	42 (7-60)	2.4 (0-4)	0	10 (6.4-13.4)	4.4 (1.0-618)
II	18	31	46 (34-70)	2.8 (2-3)	1.1 (1-2)	9.5 (5.6-12.2)	5.9 (4.2- 8.6)
III	9	15.5	42 (25-53)	2.5 (1-4)	1.8 (1-2)	9.0 (3.8-11.6)	8.2 (3.8-11.0)
IV	21	36	42 (21-55)	3.0 (1-4)	2.6 (1-4)	11.0 (3 -16.0)	9.3 (3.0-14.4)
Total	58	100					
Outpatients							
I	14	36	54 (40-60)	2.0 (1-3)	0	6.0 (2.2-10)	2.8 (0 - 5.8)
II	15	38	48 (31-63)	2.7 (2-4)	1.0 (0-1)	7.6 (3.6-11)	4.9 (2.0- 8.6)
III	7	18	45 (31-54)	3.0 (1-4)	2.0 (1-3)	8.1 (3.8-11)	6.9 (2.6-916)
IV	3	8	51 (50-52)	2.0 (1-3)	2.0 (1-3)	7.1 (4.6- 8.6)	7.1 (46- 8.6)
Total	39	100					

TABLE 3.—*Distribution of Response Groups by Clinical Classification*

Classification	Total No.	Response Group			
		I	II	III	IV
Early essential	15	8	3	2	2
Severe essential	35	5	13	9	8
Malignant	29	6	11	1	12
Renal	9	1	1	3	4
Diencephalic	8	1	5	2	0
"Ancestral"	19	9	6	0	4
Sympathectomized patients	12	3	3	4	2
All	97	24	33	16	24

sympathectomized patients are unusually susceptible to the effects of "apresoline."[6] This was not our experience; the proportion of those who had sympathectomies and who were considered as good responders to "apresoline" (6 of 12) was much the same as that for the series as a whole.

The eight case reports with accompanying graphic records appended illustrate the varieties of response and the course of the study in the inpatients and the outpatients. They demonstrate also the varying intervals of days or weeks which may elapse before antipressor effects are observed and the fact that patients with relatively few signs of advancing vascular disease may fail to respond, while others with very severe disease sometimes respond well.

6. Schroeder, H.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation 5:28, 1952.

Effect of Treatment on Severity Index.—Severity indices were reduced by treatment in Response Groups I and II. In hospitalized patients, the pretreatment index of Group I averaged 10 (6.4 to 13.4) and decreased to 4.4 (1.0 to 6.8) and that of Group II decreased from 9.5 (5.6 to 12.2) to 5.9 (4.2 to 8.6); the changes were slight in hospitalized Groups III and IV, respectively 9.0 to 8.2 and 11.0 to 9.3. Comparable improvement occurred in outpatients.

Among the panels in severity index other than blood pressure, evidences of improvement were particularly manifest in cerebral findings (Table 4). Retinal arteriolar constriction lessened, and retinal hemorrhages disappeared. Subjectively, in Groups I and II, hypertensive headaches, giddiness, paresthesias, transient pareses and encephalopathies remitted; these were also lessened in severity in Group III. We did not attempt to measure the relative alacrity of mental function in patients with extensive cerebrovascular disease; still, it was often apparent to other patients, to relatives, and to physicians that this function improved as blood pressure decreased; patients who had experienced periodic dysarthria or mental lapses were no longer subject to these disturbances.

TABLE 4.—*Means of Effect of Treatment on Estimates of Vascular Status*

	Cardiac		Renal		Cerebral	
	Mean Index		Mean Index		Mean Index	
Response Groups	Pre	Post	Pre	Post	Pre	Post
I	1.4	1.0	1.7	1.3	2.2	1.1
II	1.6	1.4	1.8	1.6	2.3	1.6
III	1.9	1.7	1.8	1.8	2.0	1.7
IV	2.4	2.5	2.6	2.7	2.5	2.5

The relative improvement in renal status was less marked than were changes in blood pressure or cerebrovascular function. The evidences of active and progressive nephrosclerosis, such as abnormal hematuria and proteinuria, were often partly or wholly remitted in good responders (Cases 1, 2, and 6); in some (Cases 1 and 2) there were gains in renal blood flow and filtration rate. No gains occurred in any of these functions in Group III, and they were progressively impaired in Group IV.

The evidences of hypertensive heart disease were generally little altered and were sometimes accentuated; patients who required salt restriction and digitalis before treatment maintained these requirements during therapeutic responses to "apresoline"; in two, congestive failure became manifest for the first time during treatment. The change in the index of cardiac status in Group I (1.39 to 1.0) was small as compared with the change in cerebrovascular index (2.17 to 1.13). It was of the same order as the change in the index of renal status, but the cardiac functions considered cannot, as in the case of the kidney, be considered largely irrecoverable. Reduction of blood pressure to normal was attended by angina pectoris of effort in two men, respectively 50 and 59 years of age; in these, when administration of the drug was discontinued or the dose decreased so that diastolic pressure rose above 100 mm. Hg, the angina disappeared. In one man of 49, an anteroseptal myocardial infarct developed (electrocardiographically demonstrated) while his blood pressure was being maintained at a near-normal range; from this he recovered. A man of 50 and a woman of 51 died suddenly, presumably from myocardial infarction.

The course of a man of 49 illustrates the problem of cardiac disability during "apresoline" treatment. In April of 1951, the average of his blood pressures was 205/125. He had no symptoms or physical signs of heart disease, and his heart size was normal, although the electrocardiogram showed a strain pattern. After administration of "apresoline" was started, he began to complain of palpitation and his heart size increased to 112% of normal. After eight weeks, the average of blood pressures was 170/104 and his cardiac status unchanged. Eight months later, the blood pressures were 160/104. The heart size was 115% of normal; he had begun to complain of angina of effort; the electrocardiogram revealed an anteroseptal myocardial infarct. Three months later, while treatment was being continued, blood pressures averaged 157/106; the heart size was 120% of normal, angina and electrocardiographic abnormalities persisted, and an apical systolic murmur had developed.

Some of the younger patients showed dramatic improvement in their evidences of cardiac disease, such as disappearance of gallop rhythm, decrease in heart size, and a change toward normal of the electrocardiogram. The deaths attributable to myocardial infarction occurred in patients of Response Group II. Another of this group died of a cerebral hemorrhage. The eight other patients who died during treatment were in Group IV; six of these died of uremia, one of cerebral hemorrhage, and one of ulcerative colitis.

Side-Reactions and Toxic Effects (Table 5).—Observations were recorded on 6 patients briefly treated in addition to the therapeutic test group. Of 103 patients, 32 took "apresoline" in therapeutic doses without incident. Of the 71 patients who had symptoms, 56 (79% of those showing symptoms) were uncomfortable but able to continue normal activity, while 15 (21%) were disabled and 5 (7%) unable to continue the medication.

These symptoms disappeared spontaneously or were controlled by other drugs within three to six weeks in 83% of those having symptoms; they persisted, albeit in a tolerable degree, in 10 patients during the whole course of treatment.

The character and incidence of these symptoms are summarized in Table 5. They can be considered in two categories: (*a*) vascular—attributable to "apresoline"-induced changes in circulation—and (*b*) extravascular—presumably direct toxic effects. Headache was complained of by 39% of patients treated; 18% had either periorbital or ankle edema. Palpitation (14%), giddiness (5%), and angina pectoris of effort (5%) comprised the other symptoms of vascular origin.

The extravascular side-effects were primarily gastrointestinal. Anorexia and nausea occurred in 35% and in occasional patients were so severe that 15 to 35 lb. (6.8 to 15.9 kg.) was lost before relief could be gained. Vomiting occurred in 15%; it occurred usually only during the first week, was rarely a daily occurrence, and showed no regular relationship to ingestion of the drug.

A grippe-like syndrome appeared in 12%, with malaise and muscle and joint pains and aches; in 5% the picture of an infection became complete with development of fever, usually with a temperature of 101 or 102 F., although the temperature reached 105 F. in two patients for five and eight days, respectively. The arthralgia in one patient required codeine for its relief.

Thrombophlebitis developed in four men in the veins around the external ankle malleolus, over which there appeared redness and tenderness with surrounding

edema. This persisted for five to seven days, showed no sign of either extension or recurrence, and was treated only by compression in an elastic bandage.

No serious changes occurred in the peripheral blood, although hemoglobin content was usually somewhat decreased by treatment. A fall in hemoglobin such as occurred in Case 5 from 14.5 gm. per 100 cc. before to 11.0 gm. during treatment was not infrequent; no severe anemias were observed over the 18 months of this study.

Many of the side-effects were controlled in the first instance by histamine-antagonizing agents such as diphenhydramine hydrochloride (benadryl hydrochloride®) or tripelennamine hydrochloride (pyribenzamine hydrochloride®), 25 to 50

TABLE 5.—*Side-Effects: Incidence, Nature, and Duration*

	No.	%
A. Incidence		
No symptoms	32	31
Discomfort	56	54
Disabling symptoms	15	15
Total	103	100
B. Nature		
Vascular		
Headache	..	39
Edema	..	15
Palpitation	..	14
Giddiness	..	5
Angina	..	5
Extravascular		
Anorexia, nausea	..	35
Vomiting	..	15
Malaise	..	12
Pain	..	11
Fever	..	5
C. Duration		
To 10 d	13	18
To 20 d	28	39
To 40 d	19	27
Persisted	11	16
Tolerable	6	8
Intolerable	5	7
Total	71	100

mg. with each dose of "apresoline," although some patients required ergotamine with caffeine (cafergot®) or codeine for the relief of headache. The angina pectoris which appeared in the two older patients who had sustained sharp decreases of pressure was relieved by permitting pressure to rise to levels consistent with comfort. Gastrointestinal symptoms were less troublesome when the drug was taken after food. Further relief was obtained by generous use of belladonna and phenobarbital. The arthralgias and fever were mitigated by salicylates in most cases.

COMMENT

The effectiveness of "apresoline" in some patients is shown by the fact that about one-quarter of a series of patients with a wide variety of hypertensive disease, including the most severe, attained normal levels of blood pressure as a result of its use. A third of the series attained diastolic pressures ranging from less than

100 to 110 mm. Hg. The frequent incidence of favorable responses in patients whose hypertension could be presumed to be neurogenic and the relative irresponsiveness of patients whose hypertension seemed to be renal were consistent with the concept that the drug may act in part by suppressing the central-nervous humoral-pressor mechanism.

About two-thirds of the patients experienced side-effects and toxic reactions; these nearly always remitted or were remediable within weeks. Of these the patient had to be forewarned, and they had to be promptly recognized and sympathetically treated as they appeared. Otherwise, the patient's cooperation in the eight weeks of clinical trial would have been jeopardized. Only about 1 patient in 20 found these reactions intolerable and was forced to discontinue use of the drug. Some of the side-effects reflected vascular disturbances, possibly attributable to the antihistaminase action of the drug (headache, edema, flushing); others, such as palpitation and giddiness, may have reflected the tachycardia and orthostatic hypotension which commonly occurred during at least the initial phases of treatment. The gastrointestinal disturbances and the grippe-like syndrome seemed to be direct toxic effects; the mild anemia commonly observed during treatment was in some degree attributable to anorexia and impaired nutrition. Evidences of hemolysis, such as occur with phenyl hydrazine, are absent.

The beneficial effects of "apresoline"-induced normal tension on the status and progress of cerebrovascular and renal disease substantiate the point of view that hypertension is deleterious as such and that the aim of its treatment is, within reasonable limits, restoration of normal tension. The improvement was particularly apparent in those aspects of cerebrovascular disease which are associated with the imminence of cerebral hemorrhage, viz., extreme elevation of diastolic pressure, severe nuchal headaches, dizziness, retinal hemorrhages, and episodic evidences of localized circulatory failure.

In terms of the index chosen, the improvement in renal status was not as marked; this fact stemmed in part from the ability of surviving cerebral tissue to take over the function of tissues which have been damaged and also from the greater precision of methods of renal-function study. The renal indices consequently continued to reflect the damage incurred during the progress of nephrosclerosis. Nevertheless, the remission of hematuria and proteinuria and, in some patients, increases of renal blood flow testify to the cessation of nephrosclerotic activity in the good-response groups.

The comparative lack of improvement in cardiac status during otherwise satisfactory responses contrasted sharply with the effect of such procedures as sympathectomy. Thus, even without a sustained reduction of arterial pressure, sympathectomy has long been observed [7] to reverse toward normal the signs of hypertensive heart disease, so that heart failure is sometimes considered to be an indication for sympathectomy.[8] The contrast is also evident in the cerebrovascular panel, in which category the response to sympathectomy is commonly unsatisfactory and occasionally disastrous.

7. Page, I. H., and Heuer, G. J.: Medical Aspects of Surgical Treatment of Hypertension, J. A. M. A. **110**:1161, 1938.

8. Chavez, I., and Mendez, L.: Surgical Treatment of Hypertensive Heart Disease and of Heart Failure of Hypertension, Am. Heart J. **37**:523, 1949.

The disparity between the cardiac effects of sympathectomy and those of "apresoline" seem to depend on differences in the locale and degree of peripheral vasodilatation effected by each and in their effects on cardiac function. Thus, "apresoline" causes widespread vasodilation and often increases renal blood flow; total peripheral resistance is considerably decreased, suggesting extensive splanchnic vasodilatation; cardiac output is considerably increased.[9] In contrast, the vasodilatation which follows sympathectomy is limited in extent and degree and is rarely associated with notable changes in renal blood flow or cardiac output.

The cause of persistent or increased cardiac disability sometimes seen among older patients who seem otherwise to respond favorably to "apresoline" is presumably the coincidence of myocardial and coronary circulatory factors. Myocardial factors are increased cardiac output and metabolic demand together with a decreased efficiency consequent on tachycardia; the limitations on coronary circulation are those which result from tachycardia, decreased diastolic pressure, and, presumably, coronary atherosclerosis. The phenomenon is analogous to that elicited by thyrotoxicosis or fever in such patients.

These predictable hemodynamic effects of "apresoline" and the experience with it described suggest certain precautions in its administration to patients whose age suggests the likelihood of coronary atherosclerosis or who have demonstrably severe hypertensive heart disease. Among older patients, great care should be exercised in adjusting dosage so that blood pressures will not fall precipitously and, in general, not to diastolic pressures of less than 100 mm. Hg. Those patients who have severe hypertensive heart disease should receive low-sodium diets (1 gm. of sodium daily or less) and, regard being paid to the effects of digitalis on myocardial efficiency, cardiac output in the absence of failure, and heart rate, digitalization should be advantageous.

Some physicians have had the impression that tolerance to "apresoline" is at times a limiting factor in its use. This drawback was not observed with the dosages employed in this study.

SUMMARY

1. Ninety-seven patients with hypertensive disease of widely varying severity and clinical classification were treated with "apresoline" as the only antipressor drug; a quarter of the group responded by decreases of diastolic pressure to normal and a third by decreases to pressure of less than 110 mm. Hg. Thus, more than one-half responded favorably.

2. The relatively high incidence of good responses in patients whose hypertension could be presumed to be predominantly neurogenic accords with the concept that the drug may act specifically on a pathogenetic cerebral humoral pressor mechanism.

3. Pre- and post-treatment clinical status were summarized as a numerical severity index. Among the factors other than arterial pressure which entered into the index, that reflecting cerebrovascular disease showed the most improvement. In the renal panel there occurred remissions of progress of nephrosclerosis and, sometimes, increases in renal function. The average cardiac status of the group

9. Wilkinson, E. L.; Backman, H., and Hecht, H. H.: Cardiovascular and Renal Adjustments to a Hypotensive Agent (1-Hydrazinophthalazine: Ciba, BA-5968: Apresoline), to be published.

who otherwise responded favorably showed little improvement, although some patients obtained substantial relief of hypertensive heart disease. Deteriorations of cardiac status were not uncommon in patients of older age groups; they are attributable to the effects of the drug on the rate and output of the heart and the limitations imposed by tachycardia and coronary atherosclerosis. Consequently, for older patients, the aim should be to maintain diastolic pressure at about 100 mm. Hg. For patients with severe hypertensive heart disease, sodium restriction and digitalization are suggested as adjuncts to treatment with "apresoline."

4. Toxic and side-effects were observed in the majority of patients but were minor, transient, or remediable in most. Common side-effects of vascular origin were headache and edema, which usually responded to histamine-antagonizing agents. Extravascular toxic effects consisted principally in anorexia and nausea, and, less frequently, a grippe-like syndrome of myalgia, arthralgia, and fever.

ADDENDUM

REPORT OF CASES

Case 1 (Group I).—A 47-year-old gasoline-station operator was admitted to the Cleveland Clinic Hospital on Nov. 11, 1951, because of exertional dyspnea, ankle edema, hepatomegaly, and hypertension of 11 months' duration which had not responded to treatment elsewhere. He had passed a medical examination for life insurance four months before the onset of this illness. His father had died at 59 years of heart disease. There was no other family history suggestive of hypertension.

On physical examination, his appearance was that of a chronically ill, moderately obese middle-aged man. The retinal arterioles were constricted and sclerotic, and the fundi showed hemorrhages and exudates and 3+ papilledema. The heart was markedly enlarged; the rate was 88; the rhythm was regular; there was a Grade II apical systolic murmur; there was no gallop rhythm, and no basal pulmonary rales were heard. The liver edge was felt 10 cm. below the right costal margin in the anterior axillary line, and it was tender. There was a 1+ pretibial edema. Peripheral pulses were normally palpable.

The initial treatment was by rice diet, adequate digitalization, and mercurial diuretics. On this regimen, he lost 17 lb. (7.7 kg.). Weekly averages of control blood pressures were 213/136, 211/137 and 205/130 mm. Hg. As his heart compensated, his symptoms disappeared. Retinal hemorrhages, exudates, and papilledema diminished slightly. He was able to take "apresoline" without side-effects. With this medication, his blood-pressure readings gradually diminished; after his vascular status had apparently become stabilized, he was discharged from the hospital and was observed weekly as an outpatient.

He has since felt well, he has worked daily, and his blood pressure has decreased toward normal levels. With a subsequent decrease in the dose of "apresoline," his blood pressure-readings have increased slightly.

Case 2 (Group II).—A 28-year-old woman stenographer complained of occipital headaches. For about a year, she had awakened with these, and they had increased in severity and frequency. She had consulted a physician and was found to be hypertensive. There were no other symptoms. Her mother and father have uncomplicated hypertension. She described herself as a tense person with a considerable number of marital and family conflicts.

On physical examination, she was an anxious young woman 63¾ in. (161.93 cm.) in height and weighing 109 lb. (49.4 kg.). The fundi showed constriction 3+ and sclerosis 1+; there were no hemorrhages or exudates, but there was papilledema 1+. The heart was not enlarged; the apex impulse was forceful; there were no murmurs or irregularities; the aortic second sound was greater than the pulmonic second sound; all peripheral pulses were well felt. There were no signs of congestive cardiac failure.

She was admitted to the hospital on Aug. 16, 1951. During the control period, successive weekly blood-pressure averages were 214/137, 187/125, and 191/125. Her headaches were extremely troublesome but responded to intravenous injection of thiocyanate. Administration

of "apresoline" was started at a dose level of 50 mg. four times a day. When the dose was increased to 75 mg. four times a day, headaches became so severe that the medication was discontinued for two days. Subsequently, the dose was slowly increased over a five-week period to a level of 300 mg. four times a day. Side-effects of headache, nausea, occasional vomiting, and anorexia persisted. During the first eight weeks of treatment, she lost 15 lb. (6.8 kg.); with decrease of the dose to 150 mg. four times a day, her appetite returned and she began to regain the weight she had lost. The blood pressure fell slowly; it only began to decrease at about the

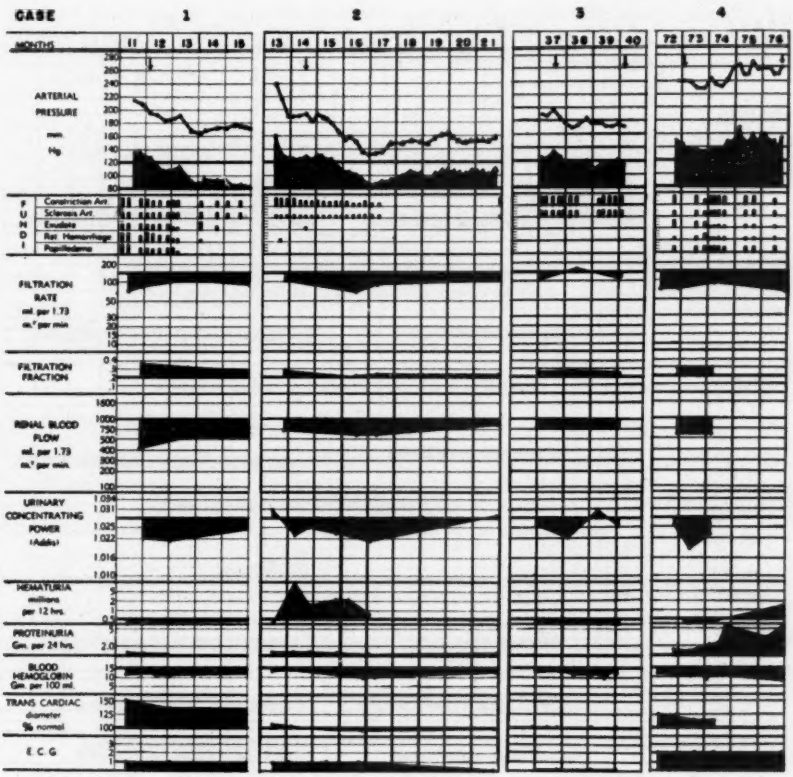

Fig. 1 (Cases 1 to 4).—The arrows at the top of these graphic charts of observations indicate the beginning and, when repeated, the end of treatment. Blood pressures indicated are casual (open circles), averages of pressures in the hospital (closed circles), and averages of pressures self-taken at home (triangles). Pretreatment severity indices of these patients were respectively 10.6, 8.6, 12.8, and 14.4; corresponding post-treatment estimates were 5.4, 2.6, 11.2, and 14.4.

5th week and did not reach a floor for 11 weeks. She was discharged receiving a dose of 150 mg. four times a day after four months of hospitalization. She has felt well except for extreme psychic tension with ill-defined fears. Although blood-pressure averages have been reduced, they are not maintained at the levels found in the hospital.

CASE 3 (Group III).—A 31-year-old white woman first came to the Cleveland Clinic on Oct. 16, 1950, for evaluation of hypertensive disease. One year previously, her first pregnancy had been terminated at the seventh month because of specific toxemia of pregnancy characterized

by hypertension, retinopathy, proteinuria, oliguria, and edema. After recovery from this episode, her blood pressure had remained elevated. Proteinuria had disappeared. Her general health had been good, but she tired easily. Her mother, who died at 59 years of atypical pneumonia, also had had hypertension. Her father died at 75 years of a stroke.

On physical examination, she seemed to be a well-developed, well-nourished woman. The retinal arterioles were markedly constricted. There was arteriolar sclerosis 2+. There were many old scars, and the right macula was obliterated by one of these. There was no papilledema.

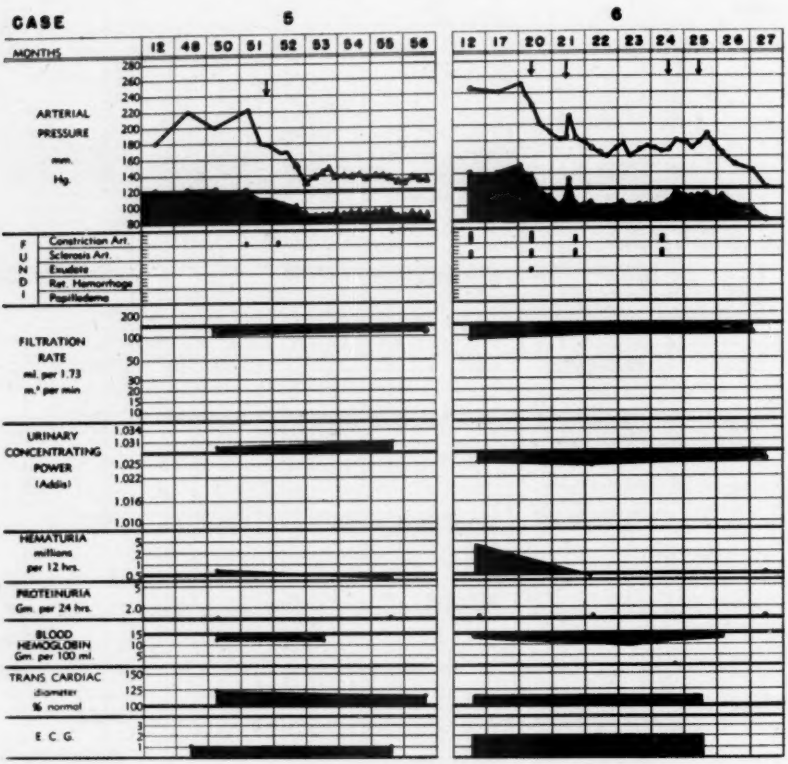

Fig. 2 (Cases 5 and 6).—The first arrows in these graphs of observations indicate the beginning of treatment; in order, succeeding arrows (Case 6) indicate the substitution of a placebo for "apresoline" for one week, a decrease in "apresoline" dosage and an increase in dosage. Blood-pressure symbols in Case 5 are: open circles, casual observations; a continuous line, averages of control observations on Patient 5 as an outpatient, and open triangles, subsequent averages of self-measured pressures. In Case 6, the open circles are averages of observations made three times weekly while the patient was attending the clinic as an outpatient. Pre- and post-treatment severity indices were 2.7 and 0 (Case 5) and 8.8 and 3.6 (Case 6).

The heart was not enlarged; there were no murmurs, no evidences of failure, and no abnormalities of pulse.

She was treated at first with akavervir (veriloid®), but because of the difficulty in controlling the side-effects, she was admitted to the hospital on Oct. 27, 1951, for reevaluation and further treatment of her hypertensive vascular disease. At this time, no further objective changes were demonstrable.

After a three-week control period, successive blood-pressure averages were 180/124, 188/122, and 198/132. Side-effects from "apresoline" consisted of frontal headache, muscle aching, and anorexia. These were largely controllable, so that after being given "apresoline" for nine days, she was receiving 300 mg. four times a day. Because of the persistence of anorexia, the doses were decreased to 200 mg. each, and all symptoms disappeared.

During the period of treatment, her blood-pressure readings declined slowly; the lowest averages obtained occurred during a bout of "flu" and associated fever. Because a favorable response was not obtained, use of "apresoline" was discontinued after 11 weeks.

CASE 4 (Group IV).—A 43-year-old woman was first seen at the Cleveland Clinic on Nov. 6, 1951, complaining of high blood pressure and nervousness. Six years before, during her last pregnancy, labor was induced because of elevated blood pressure and proteinuria. Five years

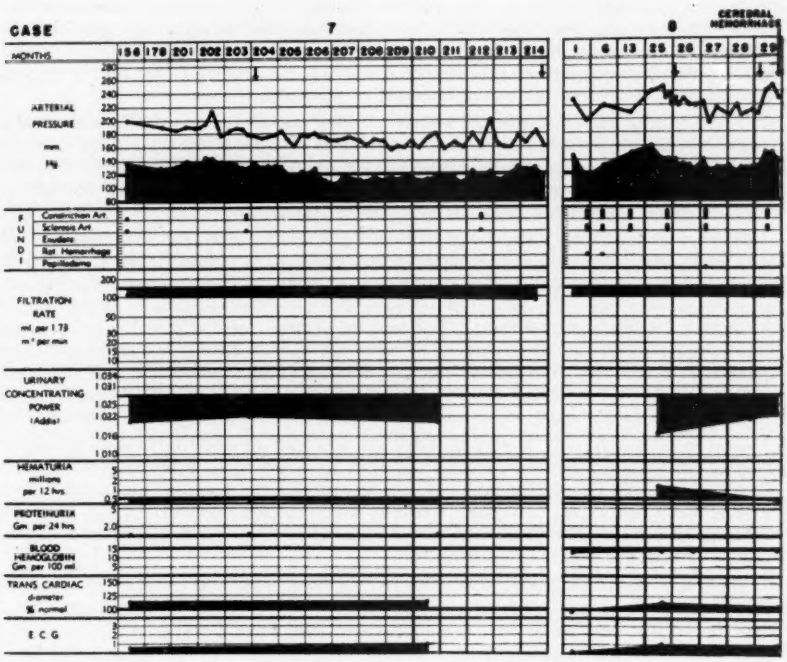

Fig. 3 (Cases 7 and 8).—The arrows in these graphs of observations indicate, respectively, the beginning and end of "apresoline" treatment; blood pressures are averages of biweekly observations on the patients as outpatients. Respective severity indices were 14 and 14.8 before treatment and remained unchanged.

later she had blurred vision for several weeks and one episode of paroxysmal nocturnal dyspnea. Recent complaints had been exertional dyspnea, nocturia of two months' duration, and a weight loss of 30 lb. (13.6 kg.) in 15 months.

One sister died of a stroke at the age of 40. There was no family history of vascular disease.

On physical examination, her appearance was that of a chronically ill, moderately obese, middle-aged woman. The fundi showed constriction 3+, sclerosis 2+, hemorrhage 1+, exudates 3+ and papilledema 2+. The blood pressure was 264/166 mm. Hg. There was a pulsus alternans. The left border of cardiac dullness was 14 cm. from the midsternal line; the apex impulse was heaving. The cardiac rate was 124; the rhythm was regular; there were a protodiastolic gallop and a Grade II apical systolic murmur. There was no pretibial edema, and

no basal pulmonary rales were heard; however, on deep inspiration, the liver edge descended 4 cm. below the right costal margin in the anterior axillary line. Peripheral pulses were normally palpable.

The patient was admitted to the hospital and was treated with a low-salt diet, mercurial diuretics, and digitalis, as a result of which all her symptoms abated. During the two-week control period, averages of morning and afternoon blood pressures were 240/152 and 240/146 mm. Hg. The dose of "apresoline" was increased slowly because of the repeated appearance of side-effects, which included headache, irritability, anorexia, nausea, and vomiting. The final dose level was 200 mg. four times a day. This had no effect on blood pressure. No new hemorrhages or exudates appeared in her retinae. Those present on admission gradually decreased in number but did not completely disappear. Papilledema diminished to 2+. Proteinuria increased, and concentrating power decreased.

She was discharged after nine weeks and thereafter was seen three times weekly as an outpatient. Blood pressure levels continued to be markedly elevated; her symptoms were multiple. The hypertensive retinopathy increased. Approximately two months after discharge, signs and symptoms of severe congestive failure developed, and she was hospitalized for further therapy. Administration of "apresoline" was discontinued.

CASE 5 (Group I).—A 40-year-old woman, an office worker, came to the Cleveland Clinic Dec. 4, 1951, for evaluation and treatment of high blood pressure of three years' known duration. Seven years before, hirsutism had developed but was well controlled with diethylstilbestrol (stilbestrol). Four years later, she was found to have asymptomatic hypertension. Her mother had had hypertension and died at the age of 63 after a stroke.

On physical examination, she was a well-developed, healthy-appearing white woman. The fundi were normal except for minimal constriction of the retinal arterioles. There was an excess of coarse hair on the face and chest. The heart was slightly enlarged; the rate was regular; no murmurs were heard. Peripheral pulses were well felt. The diagnosis of adrenal cortex hyperplasia was considered but could not be confirmed. After a control period of three weeks, administration of "apresoline" was begun; the final dose level of 100 mg. four times a day was attained in three weeks. The side-effects were transient mild anorexia and periorbital and pretibial edema. The edema disappeared spontaneously after two months. Her blood pressure fell rapidly, and the diastolic pressure has remained within normal limits for four months.

CASE 6 (Group II).—A 46-year-old housewife was first seen April 19, 1951, because of occipital headaches of four to six months' duration; these were present nearly every morning when she arose and disappeared in four to five hours. She had known of an elevated blood pressure for approximately one year. Nocturia, with urination once nightly, had developed during the past few months. There were no symptoms referable to hypertensive vascular disease. There was no family history of hypertension.

Physical examination revealed a tense, moderately obese, middle-aged woman who appeared well. There was a blotchy erythema over the neck and upper-anterior chest and upper arms. Upon funduscopic examination, the retinal arterioles were found to be markedly constricted. There was arteriovenous nicking but no hemorrhages, exudates, or papilledema. The blood pressure was 246/140 mm. Hg; the left border of cardiac dullness was 9 cm. from the midsternal line. There was a Grade II aortic systolic murmur; the aortic second sound was loud and ringing. Symptomatic treatment with aminopyrine and a head-up bed controlled the headaches for a time. However, she returned nine months later complaining of constant headache. The only change in physical findings was an exudate found in the left retina. "Apresoline" was given after a two-week control period. Side-effects consisted of headaches, palpitation, and fatigability. One month after starting medication, she was given placebo for three days and her blood pressure rose to 210/130 mm. Hg, and side-effects disappeared. After the medication was resumed, her blood pressure fell to previous levels. At a dose level of 500 mg. daily, her blood pressure was well maintained so that all diastolic levels were below 100. When the dose was decreased to 400 mg. a day, her diastolic blood pressure varied between 110 and 120, but as the medication was increased to 500 and then to 600 mg. a day, her blood pressure fell to the previous levels. During the five months of treatment, the intensity of the side-effects has gradually diminished.

CASE 7 (Group III).—A 44-year-old business man was first seen at the Cleveland Clinic in April, 1947. Hypertension, proteinuria, and cylindruria had been detected 13 years before. Other symptoms were occasional occipital headaches and nocturia, with one or two urinations, for approximately 10 years. There was no family history of hypertensive disease.

Upon examination, the blood pressure was 200/140 mm. Hg; there were retinal arteriolar constriction and sclerosis and one small area of exudate in the left eye. The apical impulse was forceful; the left border of cardiac dullness was 9.5 cm. from the midsternal line in the fifth left intercostal space. Urine cultures were negative. An Addis examination showed a concentrating power of 1.019; 0.38 gm. of protein in 24 hours; and 300,000 casts, 1,800,000 red cells, and 1,000,000 white cells in 12 hours.

Veriloid was tried ineffectively for five months beginning in November, 1950, and a course of 688-A (N-phenoxyisopropyl-N-benzyl-β-chloroethyl-amine hydrochloride) was similarly ineffective. In May of 1951, administration of "apresoline" was begun; the effect on his blood-pressure levels was slight but definite. He was able to take 600 to 700 mg. a day without side-effects save for a slight decrease in exercise tolerance. Seven months after the medication was begun, transient arthralgia which became increasingly troublesome developed; it was not controlled by histamine-antagonizing agents or acetylsalicylic acid or relieved by decreasing "apresoline" dosage. It disappeared during a short period with use of a placebo. The intensity of this side-effect being balanced against the slight therapeutic gain, administration of "apresoline" was discontinued.

CASE 8 (Group IV).—A 45-year-old real-estate salesman was first seen at the Cleveland Clinic in November, 1949, complaining of severe occipital headaches and easy fatigability. One year previously, he had had a physical examination and no mention had been made of an elevated blood pressure. Both parents had died of infections when the patient was very young; his childhood had been exceedingly unhappy; his adult life had been fraught with fears and much marital discord. His blood pressure was 250/150 mm. Hg. There was marked narrowing of the retinal arterioles. The heart was not enlarged; there were no murmurs. In the next two years, his symptoms gradually increased. Because the heart size was increasing and because of one episode of severe dizziness, nausea, and vomiting, "apresoline" therapy was started. During the four months that he took this medication, the blood pressure was not altered. His symptoms continued, but he was able to take up to 800 mg. of "apresoline" daily without side-effect. The medication was discontinued when a subarachnoid hemorrhage developed.

STUDIES OF SODIUM AND POTASSIUM METABOLISM IN SALT-LOSING NEPHRITIS

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SINCE THE term "salt-losing nephritis" was introduced by Thorn, Koepf, and Clinton [1] in 1944, in their study of two cases simulating adrenal cortex insufficiency, four additional cases have been reported.[2] An associated tendency toward excessive loss of potassium was found in one case,[2c] and electrocardiographic evidence of hyperpotassemia was seen in another.[2d] The present report is concerned with a case of salt-losing nephritis, followed for two years, in which sodium was lost and potassium was retained in excess quantities.

REPORT OF A CASE

J. B., a 30-year-old man, was first admitted to the hospital on June 19, 1950, with complaints of weakness for one year; periodic vomiting before breakfast and intermittent bleeding from the gums for three months, and occasional hematemesis, nocturia, paresthesia of hands and feet, and cramping of the calf muscles for six weeks. The patient was anorexic and had been vomiting frequently just prior to admission.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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The past history was negative for symptoms of pyelonephritis or glomerulonephritis. Hypertension was never discovered at any time. There was no family history of hypertension or renal disease.

Physical examination revealed a chronically ill white man with dehydration and pallor of the skin and mucous membranes. The temperature was 98.6 F., pulse rate 94 per minute, and respirations 20 per minute. Examination of the eyes, ears, nose, and throat gave negative results. There was no evidence of hypertension in the retinae. The lung fields were clear, but the respirations were deep and prolonged. No cardiac murmurs were audible, and the heart was not enlarged. The systolic blood pressure was 104 mm. Hg and the diastolic 60 mm. Hg. Examination of the abdomen gave negative results as did that of the extremities and genitalia.

Laboratory examination revealed a white blood cell count of 14,000 per cubic millimeter with 70% polymorphonuclear leucocytes, 13% lymphocytes, 6% monocytes, and 2% eosinophiles. The red cell count was 2,170,000 per cubic millimeter, and the hemoglobin 7.7 gm. per 100 ml.

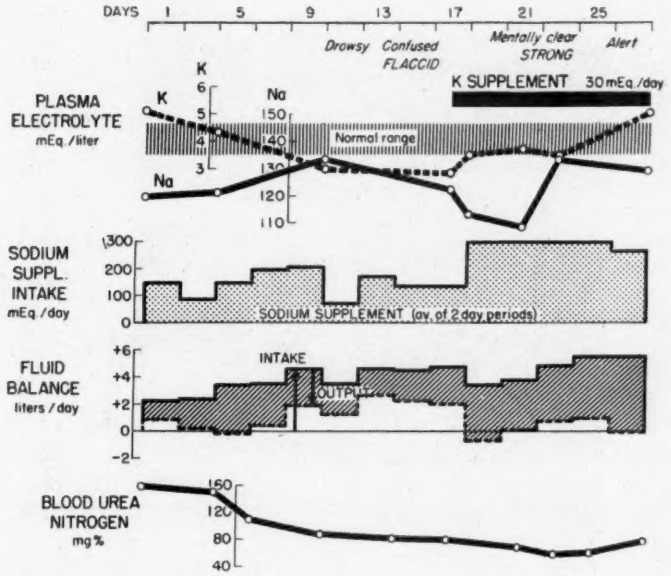

Fig. 1.—Development of hyponatremia and hypopotassemia during treatment of uremia in salt-losing nephritis.

The blood nonprotein nitrogen was 159 mg. per 100 ml. and the plasma carbon dioxide-combining power 14.4 mEq. per liter. The plasma sodium concentration was 120 mEq., serum potassium 5.1 mEq., and serum chloride 83.2 mEq. per liter. Urinalysis revealed a fixed specific gravity of 1.008 to 1.010, a trace of albumin, and occasional white and red blood cells per high-power field. Urine cultures were negative. Roentgenograms of the long bones were negative, and an intravenous pyelogram revealed no concentration of the dye. Specific renal function tests performed during the 52d week of observation revealed the glomerular filtration rate to be 4 ml. a minute, the renal plasma flow 29.1 ml. a minute, and the maximal tubular capacity for excretion of paraaminohippurate (TmPAH) 5.2 mg. a minute.

The course during the first 28 days after admission is illustrated in Figure 1. During the first ten days of therapy with an average supplementary daily intake of 175 mEq. of sodium, zero intake of potassium, and 3,300 ml. of fluid, there was a gradual improvement in the degree of azotemia, with a fall in blood nonprotein nitrogen concentration from 159 to 89 mg. per

100 ml. The plasma sodium concentration rose from 120 to 133 mEq. per liter, but the serum potassium concentration fell from 5.1 to 3.0 mEq. per liter. During the next eight days, with an average sodium intake of 134 mEq. and fluid intake of 4,400 ml. a day, there was a continued decrease in azotemia, but at the same time a severe hyponatremia developed with a plasma sodium concentration of 122 mEq. per liter on the 18th hospital day and 113 mEq. per liter on the 20th day.

Although potassium intake was practically nil during this period, the serum concentration fell only slightly, to 2.9 mEq. per liter on the 18th day. The symptoms of hypopotassemia, however, became manifest, and the patient rapidly approached an extremely critical state, with mental confusion and flaccid paralysis of all extremities. Electrocardiographic evidence of hypopotassemia also became evident (Fig. 2). The patient became moribund and required periodic artificial respiration. Since potassium drugs for parenteral administration were not readily

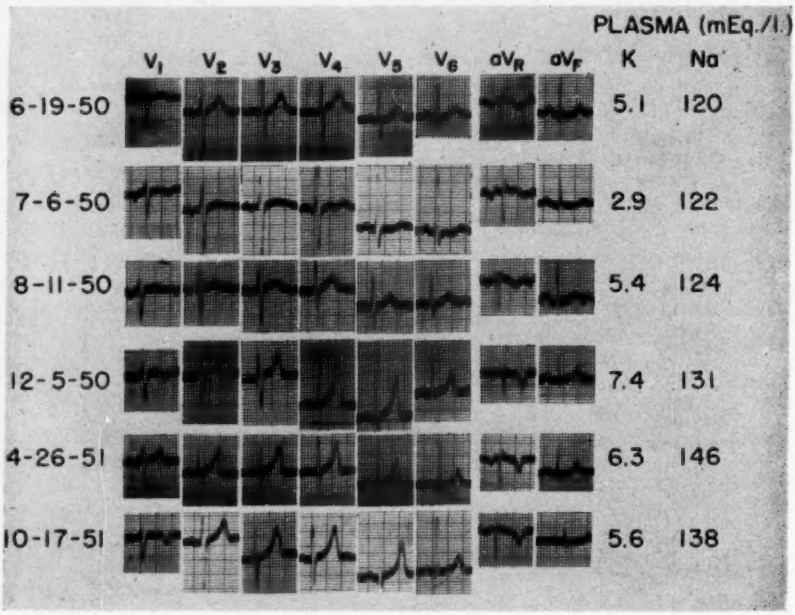

Fig. 2.—Electrocardiographic tracings correlated with the plasma potassium and sodium concentrations.

available, potassium chloride tablets were given orally. Most of the medication remained in the oral cavity, but some was swallowed. After this therapy respirations became spontaneous and the patient improved dramatically.

Potassium chloride supplements were then administered and the patient was given milk and orange juice in an effort to control the hypopotassemia. Saline infusions were also increased, so that a total of 300 mEq. of sodium a day was given as a supplement. With these measures the patient became mentally clear and alert again and the muscle strength returned to normal. The serum potassium level rose gradually to 3.7 mEq. per liter on the 22d day and to 5.1 mEq. per liter on the 29th day. The plasma sodium level rose to 130 mEq. per liter after falling transiently to 108 mEq. per liter on the 22d day. There was, in addition, a significant increase in urine output, with further decline in blood nonprotein nitrogen level.

The remainder of the course, extending over a period of 101 weeks, is summarized in the table. Attempts to lower the blood nonprotein nitrogen level by forced intake of 5 to 6 liters

Summary of Laboratory and Clinical Data and the Therapeutic Regimen During Twenty-Four Months' Follow-up

Date	Serum: Plasma Na mEq./L	Serum: K mEq./L	Serum: Cl mEq./L	Plasma CO_2CP mEq./L	Blood: NpN Mg./100 Ml.	Blood: Hgb. Gm./100 Ml.	Urine: Na mEq./Day	Urine: K mEq./Day	Clinical Observation	BP	Therapeutic Regimen
6/19/50	120	5.1	83.2	14.4	159	7.7	...	..	Admitted: nausea, vomiting, dehydration, confusion	104/60	Average daily intake Na 175 mEq./L, K none, fluid 3,300 ml.
6/29/50	133	3.0	90.6	20.7	89	...	...	..	Improved hydration and azotemia	100/60	Average daily intake Na 134 mEq./L, K none, fluid 4,400 ml.
7/ 6/50	122	2.9	79.3	22.5	82	...	...	..	Weakness, resp. paralysis, coma, artificial resp.		KCL administered
7/ 7/50	113	3.5	....	....	...	...	...	..	Dramatic improvement; spontaneous resp.		K, 30 mEq./day, Na 300 mEq./day
7/10/50	108	3.7	91.5	....	68	7.0	...	..			
7/12/50	133	3.4	101.7	....	59	...	...	..	Steady improvement		
7/17/50	129	5.1	100.0	....	75	...	484	56		130/85	
7/18/50	122	4.8	....	....	73	...	...	..	Ambulatory, eating well		Unrestricted diet, Na suppl. 300 mEq./day
7/21/50	140	6.3	....	....	99	10.5	...	..			
7/24/50	132	6.1	....	....	...	...	266	58			
8/11/50	123	5.4	101.7	....	123	9.5	352	58			
8/14/50	129	5.2	111.1	....	126	...	...	..			Forced fluid intake 5-6 L/day
8/17/50	117	5.7	98.5	....	119	...	286	38	Water intoxication with convulsions		Restricted fluid 2.5 L/day, Na 470 mEq./day
8/19/50	123	4.2	100.8	....	71	8.3	...	..	Improvement; mental clearing		
8/29/50	139	...	111.0	....	133	...	...	..			Maintenance Na suppl. 300 mEq./day
9/ 1/50	139	...	114.0	....	86	...	...	..			
9/15/50	137	6.8	....	....	...	...	...	..			
9/21/50	133	6.9	....	....	86	...	...	..			
10/ 2/50	134	6.4	....	....	84	...	...	..			
11/ 2/50	129	6.0	....	....	...	...	...	..		130/80	
11/27/50	132	6.6	110.0	12.6	148	6.5	...	..			
12/ 5/50	131	7.4	....	9.0	156	...	...	..	Relatively asymptomatic		Low K diet approx. 37.5 mEq./day with NaCl suppl.
12/20/50	126	6.8	91.0	12.1	158	...	296	38	Working periodically		300 mEq./day and $NaHCO_3$ suppl. 48 mEq./day
1/ 3/51	131	5.4	100.0	17.9	158	...	...	..			
1/16/51	126	4.6	....	....	...	...	...	..			
2/ 5/51	126	5.4	102.0	22.5	77	...	...	..			
2/21/51	138	5.4	....	14.4	146	...	344	41			Increase of $NaHCO_3$ suppl. to 60 mEq./day
3/ 7/51	123	5.8	....	19.8	142	9.0	...	..			
4/26/51	146	6.3	87.5	16.6	151	5.8	378	49			
5/29/51	134	7.4	....	....	...	6.0	...	..	Thorn test: eosin. count 344 to 139/mm.^{3} in 4 hr.		
6/ 5/51	132	6.9	....	18.4	...	...	370	49	GFR 4 ml./min.; RPF 29.1 ml./min.; TmPAH 5.2 mg./min		
6/13/51	130	5.4	....	....	...	...	...	..	PSP none in 2 hr.		
6/21/51	136	5.8	85.0	17.9	110	6.6	...	..			Desoxycorticosterone acetate 10 mg./day for 5 days
6/25/51	...	...	....	....	...	...	407	48			
6/26/51	139	6.0	....	....	...	...	373	50			
6/27/51	138	5.8	....	....	...	...	471	50			
6/29/51	135	5.8	....	....	...	...	373	50	No response to desoxycorticosterone therapy		
6/30/51	134	...	97.6	17.9	148	5.7	313	46			
7/16/51	136	6.1	103.0	17.5	160	6.8	312	49		130/80	
8/ 1/51	131	6.1	106.0	15.3	129	5.5	...	..			
8/17/51	147	5.3	....	....	...	...	301	32			Controlled K intake 25 mEq./day
8/20/51	135	4.1	....	....	...	...	...	..			
8/24/51	134	6.0	....	....	...	...	325	31			Controlled K intake 50 mEq./day
9/27/51	136	5.7	108.0	17.9	154	...	369	33			
9/19/51	139	7.0	....	....	....	8.5	...	..	Relatively asymptomatic but not working		Controlled K intake 37.5 mEq./day
9/26/51	146	4.9	96.0	17.9	...	...	...	..	Recurrent episodes of vomiting and weakness		Continued low K intake, NaCl 273 mEq./day plus
10/17/51	138	5.6	....	....	...	...	447	32			$NaHCO_3$ 60 mEq./day
2/19/52	141	5.3	86.8	23.4	159	7.0	...	..			
4/16/52	125	6.4	98.5	13.0	123	6.3	...	..		150/110	
4/29/52	132	6.8	....	8.1	...	...	...	..		110/80	
5/20/52	142	4.8	....	....	...	...	...	..	Muscular twitching and cramps, confusion		Calcium gluconate average 4.2 gm./day
5/26/52	135	6.4	99.0	12.1	122	...	...	..	Death during hypocalcemic convulsion		Calcium gluconate 5.6 gm./day

of fluid plus 18 gm. of salt a day during the ninth week resulted in a classic episode of water intoxication accompanied by delirium and convulsions. The plasma sodium level had fallen during this period to 117 mEq. per liter. The alarming symptoms were immediately relieved with 2,000 ml. of isotonic sodium chloride solution given intravenously and then controlled by restricting water to 2.5 liters and increasing sodium chloride intake to 27 gm. a day.

The patient was then maintained on 18 gm. of sodium chloride supplements a day together with a diet unrestricted in its sodium and potassium content. Under this regimen during the 11th to 25th week of observation, the plasma sodium concentration fluctuated between 128.6 and 141.5 mEq. per liter, but usually remained well below 134 mEq., confirming the diagnosis of a salt-losing type of nephritis. The serum potassium concentrations, on the other hand, were consistently in the toxic range, rising to 7.4 mEq. per liter during the 25th week. The electrocardiographic tracings taken during this week showed typical changes characteristic of hyperpotassemia (Fig. 2).

Beginning with the 26th week the patient was placed on a diet unrestricted as to sodium but limited as to its potassium content. In addition, because of the low plasma carbon dioxide-combining power of 9.0 mEq. per liter observed during the 25th week, 4 gm. of sodium bicarbo-

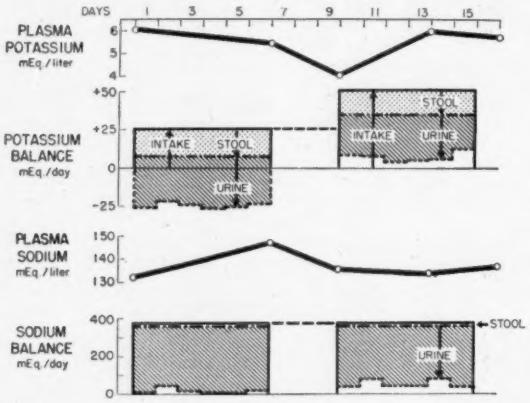

Fig. 3.—Effect of variation in potassium intake in sodium-losing, potassium-retaining nephritis.

nate supplement were added to 18 gm. of sodium chloride. Under this management the serum potassium concentration fell to subtoxic levels with improvement in the electrocardiographic picture, and the plasma carbon dioxide-combining power rose to 22.5 mEq. per liter.

A four-hour Thorn test [3] using 25 mg. of adrenocorticotropic hormone resulted in a normal fall in the total eosinophile count from 344 to 139 per cubic millimeter, indicating an adequately functioning adrenal cortex. In order further to rule out the possibility of adrenal cortex insufficiency as the cause of excessive sodium loss, a therapeutic trial of desoxycorticosterone acetate was carried out. With the use of 10 mg. a day for five days, no beneficial effects were noted in regard to urinary sodium and potassium excretions, plasma sodium and serum potassium concentrations, body weight, and blood pressure.

The development of hyperpotassemia superimposed on a tendency toward hyponatremia prompted an investigation of the potassium metabolism. The patient was studied for a total of 15 days on a constant diet containing 25 mEq. of potassium and 34 mEq. of sodium, together with daily supplements of 275 mEq. of sodium chloride and 71 mEq. of sodium bicarbonate.

3. Thorn, G. W.; Forsham, P. H., and Emerson, K., Jr.: The Diagnosis and Treatment of Adrenal Insufficiency, Springfield, Charles C Thomas, Publisher, 1948.

Fig. 4.—Gross appearance of decapsulated surface of the kidney.

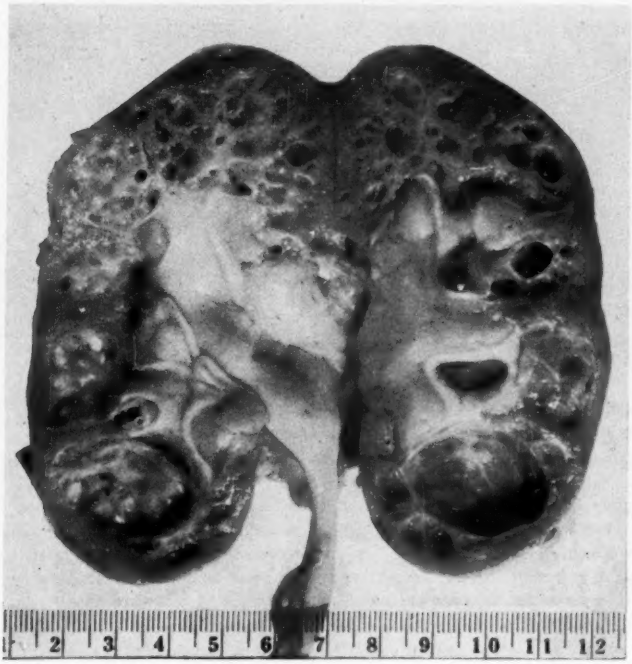

Fig. 5.—Gross appearance of sagittal section of the kidney, showing numerous cysts replacing the subcortical and medullary areas.

To compare the effect of a low potassium with that of a slightly greater potassium intake, an additional supplement of 25 mEq. (1.0 gm.) of potassium was given during the last six days of study. The results are shown in Figure 3.

With a restricted potassium intake of 25 mEq. a day, there were an average negative potassium balance of 22.3 mEq. a day and a fall in serum potassium level from 6.1 to 5.6 mEq. per liter on the seventh day of study and then to 4.0 mEq. per liter three days later.

When the total potassium intake was increased to 50 mEq. a day with supplementary potassium chloride, a slight positive balance was established and the serum level rose from 4.0 to 5.8 mEq. per liter. Throughout the periods of low and high intakes of potassium the urinary

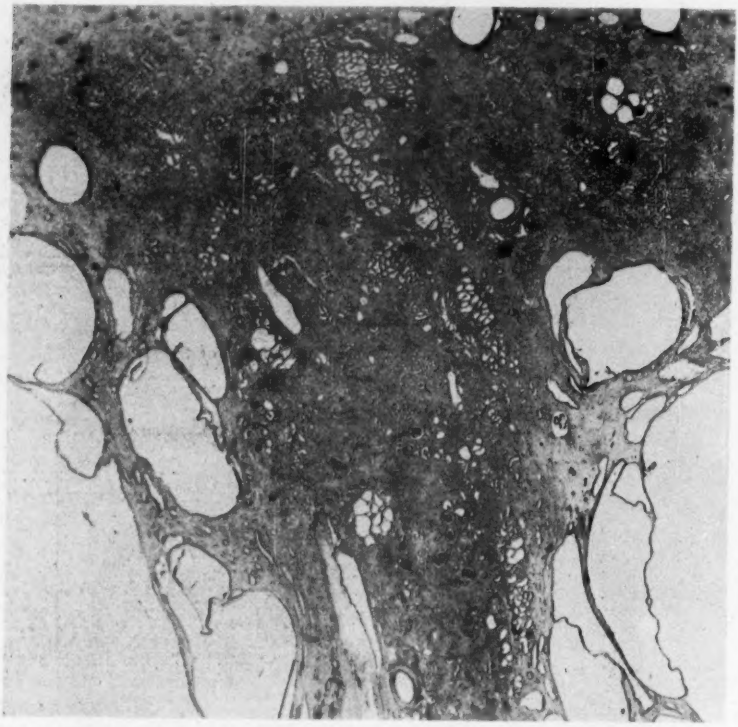

Fig. 6.—Photomicrograph of subcortical area of the kidney, showing thin-walled cysts and dilated tubules associated with marked increase in interstitial connective tissue.

concentrations of potassium remained within a narrow range, from 10 to 15 mEq. per liter, suggesting a fixed capacity for excretion of this element (isokalinuria).

The optimal intake of potassium for this patient thus appeared to be much less than 50 mEq. and probably only slightly greater than 25 mEq. a day. With a selective dietary intake of approximately 37.5 mEq. of potassium a day the serum potassium concentration fluctuated between 5.3 and 6.7 mEq. per liter. Use of 16 gm. of sodium chloride and 5 gm. of sodium bicarbonate supplements was also continued. On this regimen the patient remained relatively free of symptoms for approximately nine months except for some weakness and occasional episodes of nausea and vomiting necessitating parenteral administration of fluids and blood transfusions.

In spite of close observation and careful management the patient began to have a series of hypocalcemic convulsions which were refractory to intravenous calcium gluconate therapy, and he died in a seizure approximately 24 months after the initial hospitalization.

Autopsy was performed two hours after death.[4] The pertinent findings were limited to the kidneys, the parathyroid, and the adrenal glands. The kidneys weighed 100 gm. each and were similar in appearance. The capsules stripped readily, revealing a smooth firm pinkish-gray surface with an occasional small cortical cyst (Fig. 4). The striking change observed on section was the presence of numerous thin-walled cystic spaces varying from a few millimeters to 2.5 cm. in diameter, filled with clear colorless watery fluid, and replacing the major portion of the

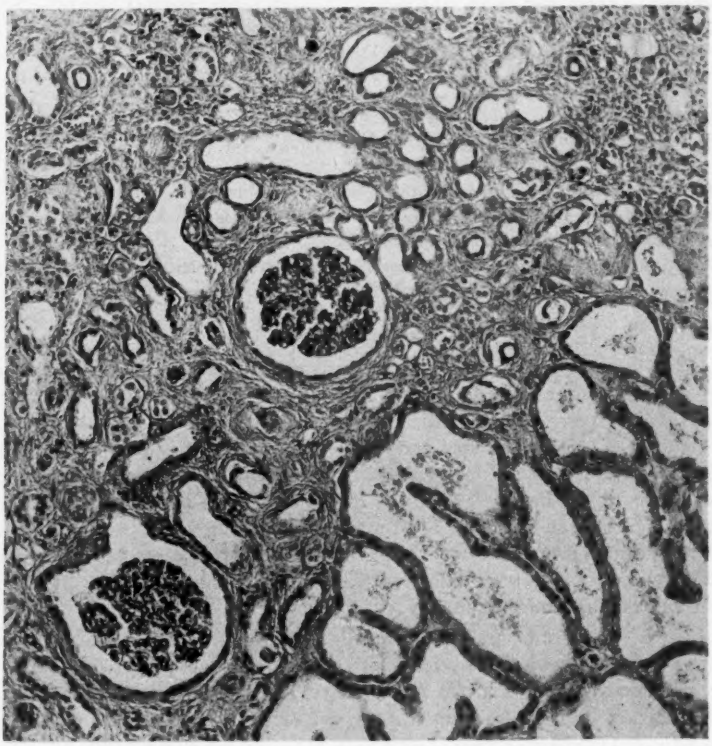

Fig. 7.—Photomicrograph of cortex of the kidney, illustrating relatively intact glomeruli with widened Bowman's spaces and subcapsular fibrosis. The proximal tubules show compensatory hypertrophy and dilatation.

subcortical and medullary areas of the kidney (Fig. 5). The cortex was relatively uninvolved and measured up to 5 mm. in thickness. The larger renal vessels were normal. The pelves and the calyces were of normal caliber, although the mucosal cysts were present in the lower pelves and the upper 2 cm. of the ureter. Calculi were absent.

Microscopically the cystic spaces were found to occupy mainly the medullary region and to be lined by flattened or low cuboidal epithelial cells (Fig. 6.) The cysts were surrounded by

4. The pathological examination was performed by Dr. John L. Langin, Department of Pathology, Veterans Administration Hospital, Dearborn, Mich.

condensed cellular fibrous connective tissue and atrophic dilated tubules. Although these cysts encroached upon the papillae to a varying degree, the collecting tubules for the most part appeared intact. In the cortex many atrophic and sclerotic glomeruli were present, accompanying a decrease in the number of apparently viable glomeruli without obvious intrinsic abnormalities (Fig. 7). The capsular spaces, however, were widened, and varying degrees of subcapsular fibrosis were noted. Focal areas of dilatation of proximal convoluted tubules lined by hyperplastic epithelium were present. The loop of Henle and the distal convoluted tubules were dilated and lined by atrophic epithelial cells. Some of these tubules were filled with a pink-staining colloidal precipitate. There was a diffuse fibrosis throughout the parenchyma with local areas of scarring and lymphocytic infiltrations. The arterioles exhibited mild to moderate medial hypertrophy, but the larger vessels were normal. The walls of the calyces and the pelves showed mild fibrosis and moderate edema with occasional lymphocytic infiltrations. Focal nests of transitional cell epithelium (Von Brunn's nests) were seen in the mucosal wall. Some of these showed early cyst formation.

All four parathyroid glands were grossly enlarged, varying in size from 5 by 5 mm. to 15 by 25 mm. Microscopically there was a diffuse hyperplasia of the chief cells.

The adrenal glands were somewhat enlarged and weighed a total of 20 gm. The cortex measured 3 mm. in thickness. Microscopically, the zona fasciculata was wide and made up most of the cortex. The contained cells were distended with lipid material.

The liver, spleen, and bone marrow showed moderate siderosis apparently due to the numerous blood transfusions which the patient had received.

The final diagnosis was chronic pyelonephritis with cyst formation, secondary parathyroid hyperplasia, and diffuse adrenal cortex hyperplasia.

COMMENT

A salt-losing tendency in chronic nephritis was first studied in 1929, by Peters,[5] who found excessive excretions of chloride ions in spite of a markedly decreased serum chloride level in two patients. However, the clinical importance of this syndrome was not appreciated until 1944, when Thorn, Koepf, and Clinton [1] described two cases of salt-losing nephritis simulating adrenal cortex insufficiency. Similar clinical studies were reported on isolated cases by Sawyer and Solez,[2a] Borst,[2b] Earle and co-workers,[2c] and recently by Nussbaum, Bernhard, and Mattia.[2d] For a comprehensive summary of the previously reported cases and a comparison of these with the present case it is perhaps most appropriate to consider the different aspects of this syndrome separately.

Etiology and Pathology.—The eitology and pathology of salt-losing nephritis in the previously reported cases have varied considerably. On pathological examination the kidneys in the first case reported by Thorn and associates [1] showed multicystic damage of the renal parenchyma apparently similar to that found in the present case. Findings in their second case, however, were characteristic of chronic glomerulonephritis. The patient reported by Sawyer and Solez [2a] also had chronic glomerulonephritis, as well as extensive calcification of the tubular membrane. The pathological findings in the case reported by Borst [2b] were those of bilateral cystic disease of the kidneys presumably congenital in origin. The patient studied by Nussbaum and co-workers [2d] was found to have had chronic pyelonephritis. The nature of the kidney lesion in the patient seen by Earle and associates [2c] was unknown, as

5. Peters, J. P.; Wakeman, A. M.; Eisenman, A. J., and Lee, C.: Total Acid-Base Equilibrium of Plasma in Health and Disease: Acidosis of Nephritis, J. Clin. Invest. **6**:517-549, 1929.

the patient was living. In the present case the kidney lesions were compatible with intrarenal obstructive pyelonephritis with extensive cyst formation. Although acute inflammatory changes were negligible, sufficient fibrous tissue was present to account for tubular obstruction and cyst formation. It is impossible at present to state whether or not a specific infection was responsible for the pathological picture and the clinical outcome. Although the disease appeared inflammatory in origin, the unknown factor of a possible congenital polycystic renal disease with superimposed chronic infection cannot be excluded. The absence of cysts in the cortical region was contrary to the usual forms of congenital polycystic kidneys.

Clinical Manifestations.—In all previously reported cases there was a history of chronic illness of several months to as long as 10 years. Weakness, weight loss, nocturia, and polyuria were consistently found, and vomiting in the morning and after meals were present in three cases.[6] The acute illness which in most cases prompted hospitalization was characterized by dehydration, mental confusion, drowsiness, and lassitude, and in one of the cases reported by Thorn, Koepf, and Clinton [1] the patient was in coma. Physical examination consistently revealed hypotension and uremic odor to the breath except in the case reported by Earle and associates,[2c] in which the blood pressure was normal and azotemia minimal. Without exception the fundi have been normal. Pigmentation of the skin was absent except for diffuse tanning in the case reported by Sawyer and Solez.[2a] The clinical manifestations in the present case were essentially similar to those reported previously. Recurrent periods of nausea and vomiting were extremely distressing and on numerous occasions necessitated hospitalization and parenteral replacement of sodium.

Laboratory Findings.—Laboratory studies in the previously reported cases of salt-losing nephritis have in general been similar. Routine urine examination characteristically revealed a fixed specific gravity of 1.005 to 1.012, absence or a trace of albumin, and no formed elements in the urinary sediment. However, in the case reported by Earle and co-workers [2c] granular casts were intermittently present. Polyuria was common, the urine volume approximating 3 to 4 liters a day in most cases. Blood studies consistently revealed severe nitrogen retention, moderate to severe acidosis, and electrolyte imbalance involving sodium and chloride. Renal function tests revealed marked impairment, with excretion of phenolsulfonphthalein below 10% in all the cases reported. In our case no dye was excreted in two hours. Urea clearances were similarly depressed. Specific renal function tests performed by Earle and associates [2c] showed a 33% decrease of glomerular filtration rate, renal plasma flow, and maximal tubular capacity for excretion of paraaminohippurate and reabsorption of glucose. Studies performed in the present case showed severe depression of all values, and consequently an accurate interpretation of the functional pattern was not possible.

Anemia was usually severe, and in the case reported here transfusions were required once a month to maintain the hemoglobin concentration at 8 gm. per 100 ml.

Disturbance in Sodium Metabolism.—In the six cases of salt-losing nephritis reported to date the amount of sodium lost in the urine was considerable and the

6. Thorn, Koepf, and Clinton.[1] Sawyer and Solez.[2a] Borst.[2b]

total amount of sodium supplements required to maintain an equilibrium varied from 205 to 350 mEq. a day (12 to 20 gm. of sodium chloride). In most cases the sodium ion was administered as chloride and bicarbonate salts together. In the case reported here a total of 334 mEq. of sodium (16 gm. of sodium chloride and 5 gm. of sodium bicarbonate) was necessary to keep the patient in a relative state of electrolyte equilibrium. Undoubtedly, the minimum requirement of sodium salts in most cases of chronic nephritis is significantly greater than in normal persons,[7] but usually this amount can be obtained through the use of dietary table salt. In the cases of salt-losing nephritis reported previously and in the case reported here such large amounts of sodium were required that the condition simulated adrenal cortex insufficiency. Therapeutic trials with desoxycorticosterone have been utilized by others [8] and by us in order to distinguish the two conditions. In the present case, 10 mg. a day of desoxycorticosterone acetate failed to alter the rate of sodium, potassium, or water excretion, thus excluding the possibility of Addison's disease as the cause of sodium depletion. The normal eosinophile response to adrenocorticotropic hormone also established the adequacy of the adrenal cortex function in this case. Needless to say, the Robinson-Kepler-Power water test [9] and the salt-deprivation test [10] would be of no value in distinguishing these two conditions.

Although it is most probable that damage to renal tubules resulting in failure of reabsorption of sodium [11] would explain the excessive loss of this element, other tubular dysfunctions, such as failure in ionic exchange between hydrogen and sodium due to excessive secretion of potassium,[12] must also be considered as possible explanations. Compensatory secretion of potassium by intact tubules in the present case may partly explain the failure of adequate reabsorption of sodium.

Disturbance of Potassium Metabolism.—Values for serum potassium in chronic renal insufficiency may be normal, increased, or decreased.[13] Hyperpotassemia usually occurs in terminal nephritis with severe oliguria but may occasionally occur with presumably adequate urine volume.[14] Marked retention of potassium, with its toxic effect upon the myocardium, has been implicated frequently as the cause of

7. Thorn, G. W.: Treatment of Renal Insufficiency, J. Urol. **59**:119-148, 1948. Peters, Wakeman, Eisenman, and Lee.[5]

8. Thorn, Koepf, and Clinton.[1] Sawyer and Solez.[2a] Borst.[2b] Nussbaum, Bernhard, and Mattia.[2d]

9. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in Recognition and Exclusion of Addison's Disease: Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:577-583, 1941.

10. Culter, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, J. A. M. A. **111**:117-122, 1938.

11. Thorn, Koepf, and Clinton.[1] Sawyer and Solez.[2a]

12. Berliner, R. W.; Kennedy, T. J., and Arloff, J.: Acidification of Urine and Potassium Metabolism, Am. J. Med. **11**:274-282, 1951.

13. Keith, N. M., and Osterberg, A. E.: The Tolerance for Potassium in Severe Renal Insufficiency: A Study of 10 Cases, J. Clin. Invest. **26**:773-783, 1947.

14. Elkinton, J. R.; Tarail, R., and Peters, J. P.: Transfers of Potassium in Renal Insufficiency, J. Clin. Invest. **28**:378-388, 1949. Keith, N. M.; King, H. E., and Osterberg, A. E.: Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, Arch. Int. Med. **71**:675-702, 1943.

death in severe renal insufficiency.[15] On the other hand, hypopotassemia has also been reported in chronic renal insufficiency,[16] and successful treatment with supplementary potassium salts has been described.[17]

Controlled studies of potassium metabolism in salt-losing nephritis have not been conducted in previously reported cases except that followed by Earle and associates.[2c] These authors described a patient in whom both sodium and potassium were lost from the body by excessive excretion through the kidney. Loss of sodium, but apparent retention of potassium, as suggested by electrocardiographic changes, were found in a case studied by Nussbaum, Bernhard, and Mattia.[2d]

In the case reported here the serum potassium concentrations were consistently elevated above normal except during the first three weeks of observation, when hypopotassemia was inadvertently induced by repeated infusions of saline and dextrose solutions. It was apparent, however, that with unlimited dietary intake there was a distinct tendency toward retention of potassium and development of hyperpotassemia, the value reaching as high as 7.4 mEq. per liter.

Controlled metabolic studies carried out in this case established the maximal tolerance of potassium to be less than 50 mEq. a day (approximately 2 gm. a day) and the minimal requirement to be greater than 25 mEq. a day (approximately 1 gm. a day). Restriction of potassium to 37.5 mEq. a day (approximately 1.5 gm. a day) partially succeeded in maintaining serum potassium concentrations at more favorable levels.

The retention of potassium in this case was most likely due to insufficient filtration, since the observed glomerular filtration rate was only 4 ml. a minute. In addition, the inability to compensate through tubular secretion may have partially accounted for the retention. In favor of the latter possibility is the correlation between the daily requirement of potassium (approximately 37.5 mEq. a day) determined by controlled metabolic studies and the calculated value of 34.5 mEq. which was filtered through the glomeruli.

SUMMARY

Most patients with salt-losing nephritis thus far reported in the literature, appear to have had no difficulty in the excretion of potassium, although in one of these [2d] electrocardiographic evidence of hyperpotassemia was found. Concomitant hypopotassemia, on the other hand, was present in the case studied by Earle and associates.[2c]

In the present case, a 30-year-old patient with salt-losing, but potassium-retaining, nephritis was studied for a total period of 24 months.

15. Keith, N. M., and Burchell, H. B.: Clinical Intoxication with Potassium: Its Occurrence in Severe Renal Insufficiency, Am. J. M. Sc. **217**:1-12, 1949.

16. (*a*) Kjerulf-Jensen, K.; Krarup, N. B., and Warming-Larsen, A.: Persistent Hypokalæmia Requiring Constant Potassium Therapy, Lancet **1**:372-375, 1951. (*b*) Davidsen, H. G.; Kjerulf-Jensen, K., and Krarup, N. B.: Treatment of Chronic Renal Potassium Deficiency, Lancet **1**:375-378, 1951. (*c*) Brown, M. R.; Currens, J. H., and Marchand, J. F.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545-549, 1944. (*d*) Tarail, R., and Elkinton, J. R.: Potassium Deficiency and the Role of the Kidney in Its Production, J. Clin. Invest. **28**:99-113, 1949. (*e*) Earle, Sherry, Eichna, and Conan.[2c]

17. Kjerulf-Jensen, Krarup, and Warming-Larsen.[16a] Brown, Currens, and Marchand.[16c]

Treatment of uremia during the initial hospitalization with large quantities of dextrose and smaller quantities of saline infusions lowered the blood nonprotein nitrogen, but at the same time produced an alarming episode of hypopotassemia and hyponatremia with generalized muscular weakness and respiratory paralysis. The response to potassium chloride salts was dramatic. It was found subsequently that 18 gm. of sodium chloride and 5 gm. of sodium bicarbonate were necessary to maintain hydration and sodium balance. In addition, metabolic balance studies, including urine and stool analyses, indicated an optimal intake of potassium somewhere between 1 gm. (25 mEq.) and 2 gm. (50 mEq.) a day. Restriction of potassium to 1.5 gm. (37.5 mEq.) a day was successful in keeping the plasma potassium concentrations near normal levels. Failure of a therapeutic trial with desoxycorticosterone and an adequate eosinophilic response to adrenocorticotropic hormone ruled out the possibility of adrenal cortex insufficiency.

The literature is reviewed for the purpose of elucidating the etiological, pathological, and clinical aspects of this syndrome.

FATAL COMPLICATIONS OF INTENSIVE ANTIBIOTIC THERAPY IN PATIENTS WITH NEOPLASTIC DISEASE

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ANTIBIOTIC agents interfere with cell division in tissue culture.[1] When given in large doses aureomycin suppresses the growth of transplanted tumors in small animals.[2] Regional intra-arterial administration of aureomycin appears to enhance the effect of nitrogen mustard (methyl-bis-[β-chloroethyl] amine hydrochloride) and irradiation on certain tumors in man.[3] For these reasons investigation of the effect of very large doses of other antibiotics (namely, terramycin and penicillin) on a few patients with neoplastic disease was undertaken.

The available reports [4] had suggested that parenteral administration of large doses of terramycin and penicillin is without hazard. However, in our studies certain grave complications were encountered. Since the patients treated had far-advanced cancer with serious complications of various kinds, drug toxicity was not

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1. Lepine, P.; Barski, G., and Maurin, J.: Action of Chloromycetin and Aureomycin on Normal Tissue Cultures, Proc. Soc. Exper. Biol. & Med. **73**:252 (Feb.) 1950. Cornman, I.: Survival of Normal Cells in Penicillin Solutions Lethal to Malignant Cells, Science **99**:247 (March 24) 1944.

2. Sokoloff, B., and Eddy, W. H.: Effect of Aureomycin on Transplanted Tumors, Federation Proc. **10**:371 (March, Pt. 1) 1951.

3. Barberio, J. R.; Berry, N.; Bateman, J. C.; Cromer, J. K., and Klopp, C. T.: Combined Administration of Aureomycin and Nitrogen Mustard: II. Effects of Intra-Arterial Administration on Human Cancer, Cancer, to be published. Bateman, J. C.; Barberio, J. R.; Cromer, J. K., and Klopp, C. T.: Investigation of Mechanism and Type of Jaundice Produced by Large Doses of Parenterally Administered Aureomycin, Antibiotics & Chemotherap., to be published.

4. (*a*) Pulaski, E. J.; Artz, C. P., and Reiss, E.: Terramycin and Aureomycin in Surgical Infections, J. A. M. A. **149**:35 (May 3) 1952. (*b*) Reiss, E.; Pulaski, E. J.; Artz, C. P., and Shaeffer, J. R.: Terramycin in Treatment of Peritonitis, A. M. A. Arch. Surg. **64**:5 (Jan.) 1952. (*c*) Whipple, R. L., Jr.: The Cure of a Patient with a Very Resistant Streptococcus Viridans Endocarditis with Massive Penicillin Therapy (Average Daily Dose of 86 Million Units), Am. Heart J. **42**:414 (Sept.) 1951.

at first suspected. Only in retrospect did it become apparent that there were certain striking similarities in the courses of these patients. A review of the literature indicates that some of the findings herein described may have been observed by others.[5] The mechanism of toxicity is not known; studies to clarify this are now under way.

MATERIALS

Thirteen patients were studied. Twelve had cancer; the diagnosis in all their cases was confirmed histologically. One patient had recently had a surgical exploration for parathyroid adenoma because of characteristic blood studies and x-ray evidence of bilateral staghorn renal calculi. Vigorous therapy with chloramphenicol (chloromycetin®), streptomycin, and sulfisoxazole (gantrisin®) had failed to eradicate a symptomatic urinary-tract infection; terramycin was therefore administered parenterally. The same symptom complex that was observed in the nine other terramycin-treated patients developed.

The intravenous route of drug adminstration was used in all cases; one patient (Case 3) also received the antibiotic through an arterial cannula directly into the tumor site. Nine patients received crystalline terramycin hydrochloride buffered with sodium glycinate in doses of 0.5 or 1.0 gm. diluted with 30 cc. of distilled water and injected slowly. In one case (Case 8) 0.5 gm. of the drug was diluted in 500 cc. of 5% dextrose in distilled water. Three patients received crystalline penicillin G potassium in doses of 12,000,000 units diluted in 30 cc. of distilled water and administered every four to eight hours.

Dornbush's method for determination of serum-aureomycin levels[6] was adapted for serum-terramycin assay. Serum-penicillin levels in Case 12 were determined by a modified Rammelkamp assay test[7] and on dogs by the method of Randall.[8] Blood nonprotein nitrogen and blood urea nitrogen were determined by the standard micro-Kjeldahl method and the method described in the War Department Manual, respectively. The method of Malloy and Evelyn was employed for serum-bilirubin determination.[9] Serum-sodium and serum-potassium determinations were made on a Perkin-Elmer flame photometer according to the method described in the Perkin-Elmer Manual.

OBSERVATIONS

Terramycin Group.—The 10 patients who were treated with terramycin (Cases 1 through 10) are listed in Table 1. There were four women and six men, with an age range of 33 to 78 years; nine had cancer. In 3 cases (Cases 4, 5, and 7)

5. (*a*) Jackson, G. G.; Haight, T. H.; Kass, E. H.; Womack, C. R.; Gocke, T. M., and Finland, M.: Terramycin Therapy of Pneumonia: Clinical and Bacteriologic Studies in 91 Cases, Ann. Int. Med. **35**:1175 (Dec.) 1951. (*b*) Womack, C. R.; Jackson, G. G.; Gocke, T. M.; Kass, E. H.; Haight, T. H., and Finland, M.: Terramycin Therapy of Urinary Tract Infections, A. M. A. Arch. Int. Med. **89**:240 (Feb.) 1952.

6. Dornbush, A. C., and Pelcak, E. J.: The Determination of Aureomycin in Serum and Other Body Fluids, Ann. New York Acad. Sc. **51**:218 (Nov. 30) 1948.

7. Done by Mrs. Susan Gougè, of Gallinger Municipal Hospital.

8. Randall, W. A.; Price, C. W., and Welch, H.: The Estimation of Penicillin in Body Fluids, Science **101**:365 (April 6) 1945.

9. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with Photoelectric Colorimeter, J. Biol. Chem. **119**:487, 1937; cited by Powell, W. N.: A Method for the Quantitative Determination of Serum Bilirubin with the Photoelectric Colorimeter, Am. J. Clin. Path., Tech. Sec. **8**:55 (May) 1944, in Am. J. Clin. Path. Vol. 14, May, 1944.

TABLE 1.—*Data on Patients Treated with Terramycin*

Patient	Age	Sex	Diagnosis	Terramycin			Nonprotein Nitrogen, Mg./100 Ml.		Direct and Total Serum Bilirubin, Mg./100 Ml.		Comment
				Gm.	Dates	Route	Before	After (Date)	Before	After (Date)	
1. B. S.	68	M	Recurrent epidermoid ca larynx; prior surgery (laryngectomy & radical neck dissection), x-ray	28.25	8/ 4 to 8/12/41	I. V.	59	329 (8/13/51)	(D) 0.3 (T) 0.466	1.23 (8/13/51) 2.00 (8/13/51)	Died in shock 8/13/51
2. M. L.	33	F	Recurrent adenoCa, breast; prior surgery, x-ray, & chest tap	14.0	7/28 to 7/31/51	I. V.	..	98 (7/30/51)	.....	.....	Had increasing thirst & restlessness; died 8/2/52; P. M. showed metastases to nodes, pleura, bone, & kidneys
3. W. L.	75	M	Recurrent ca ear with paralysis left C VII, IX, X, XI & XII; prior surgery	15.5	10/10 to 10/16/51	I. A. then I. V.	44	151 (10/18/51)	(D) 0.0 (T) 0.334	2.68 (10/18/51) 3.34 (10/18/51)	Died 10/19/51; P. M. showed extensive glomerular sclerosis in kidneys
4. C. Sh.	55	M	Epidermoid ca alveolar ridge; prior x-ray	20.0	10/11 to 10/19/51	I. V.	29	109 (10/19/51)	(D) 0.67 (T) 1.60	1.60 (10/19/51) 2.12 (10/19/51)	Radical neck dissection, resection mandible & tongue, & tracheotomy, 10/16/51; died 10/19/51; P. M. showed mediastinitis
5. B. A.	56	M	Epidermoid ca buccal mucosa with cervical-node metastases	16.0	10/20 to 10/27/51	I. V.	34	161 (10/26/51)	(D) 0.334 (T) 1.0	0.5 (10/23/51) 1.34 (10/23/51)	Radical neck dissection 10/18/51; hemorrhage from surgical site; shock; died 10/27/51
6. E. C.	78	F	Recurrent epidermoid ca ear; prior surgery (3 times)	9.0	12/ 6 to 12/10/51	I. V.	39	216 (12/14/51)	(D) 0.305 (T) 0.38	1.334 (12/14/51) 2.00 (12/14/51)	Died 12/15/51; P. M. showed extensive changes in kidneys secondary to vascular disease
7. G. G.	64	M	Ca larynx; prior x-ray	13.0	10/29 to 11/ 4/51	I. V.	29	44 (11/ 2/51)	(D) 0.134 (T) 0.668	0.532 (11/ 2/51) 1.25 (11/ 2/51)	Laryngectomy, pharyngectomy & neck dissection 10/30/51; died in shock 11/6/51
8. W. B.	44	F	Parathyroid adenoma removed 11/7/51; bilateral renal calculi; osteitis cystica; urine culture positive for Esch. coli & hemolytic Staph. aureus	4.0	12/15 to 12/18/51	I. V.	33 (BUN)	226 (12/21/51)	.....	.....	Died 12/21/51; P. M. showed almost complete fibrous replacement of renal parenchyma with lymphocytic infiltration
9. C. S.	49	M	Recurrent epidermoid ca tongue; metastases to cervical nodes; prior surgery, x-ray, & radium	26.87	9/28 to 10/15/51	I. V.	39	31 (10/16/51)	(D) 0.267 (T) 0.667	0.0 (10/16/51) 0.667 (10/16/51)	Decreased edema of jaw
10. S. W.	33	F	AdenoCa colon; metastases to liver; prior surgery; febrile course following HN_2	7.5	4/29 to 5/ 9/52	I. V.	41	46 (5/10/52)	(D) 0.500 (T) 1.00	0.667 (5/ 8/52) 1.17 (5/ 8/52)	Fever down

intravenous antibiotic therapy was part of a planned program which included surgical treatment. Terramycin administration was started prior to operation in two cases and two days after operation in the third. In all other cases of cancer the disease was incurable by present treatment methods. The total dose of terramycin ranged from 4 to 28.25 gm. given in 4 to 17 days. The pretreatment serum-nonprotein-nitrogen determination was above normal in five of eight patients, and the blood-urea-nitrogen determination was abnormal in one control specimen. During therapy, the serum nonprotein nitrogen rose significantly in 7 cases. In two cases (Cases 9 and 10) the dose of terramycin was promptly reduced when the serum nonprotein nitrogen began to rise; serious complications from therapy were not encountered in these cases. Changes in serum urea nitrogen paralleled those of nonprotein nitrogen when both determinations were made. Quantitative direct and total serum-bilirubin determinations demonstrated a slight increase in six to eight cases studied; in the two (Cases 9 and 10) in which azotemia did not develop there was no change. Pretreatment bilirubin concentrations in three cases (Cases 4, 5, and 10) were above normal, a possible reflection of the extent of disease.

A shock-like state terminated by death occurred in eight cases. In two (Cases 1 and 2) the condition on admission was considered terminal and death was anticipated. Mild postoperative bleeding occurred in one (Case 5), and a severe mediastinitis was demonstrated at autopsy in another (Case 4). Two patients (Cases 3 and 6) had advanced arteriosclerosis; this was particularly apparent in the kidneys at autopsy. For two patients (Cases 9 and 10), who were treated after the possible toxicity of the drug was realized the dose of terramycin was promptly reduced when the serum nonprotein nitrogen began to rise. Serious complications from therapy were not encountered in these two patients.

The accompanying chart illustrates the relationship of the serum-nonprotein-nitrogen concentration and arterial-blood-pressure changes to terramycin therapy. Three patients (Cases 1, 2, and 3) were hypertensive on admission. In all fatal cases there was terminal hypotension, including one (Case 8) in which the total dose of terramycin was small. The hypotension was not accompanied by other signs of circulatory collapse; the extremities were warm and dry. In two of the fatal cases (Cases 6 and 8) the serum-terramycin levels were 12.8 and 16 γ per milliliter although 85 and 49 hours, respectively, had elapsed since administration of the last dose of drug. In contrast, the serum-terramycin level was only 0.8 γ per milliliter 21 hours after completion of therapy in a surviving patient (Case 9) who had received a much larger total dose of terramycin.

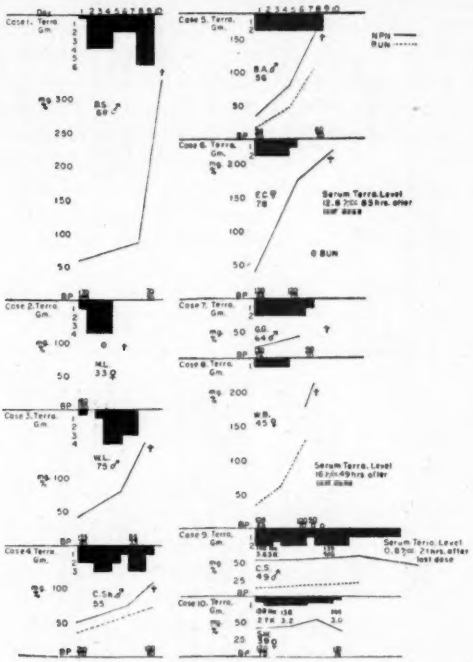
Serum-sodium and serum-potassium determinations were done in two nonfatal cases (Cases 9 and 10). In one of these (Case 10), 20 mEq. of potassium in an infusion of dextrose was given by the intravenous route on the second, third, and fourth day of therapy because of an initial low serum-potassium level. No significant changes in serum-electrolyte levels were seen during therapy.

Severe nausea and vomiting were observed in one case only (Case 2). Diarrhea did not occur. Anuria and oliguria did not develop in any of these patients. Unusual thirst was frequently present.

Postmortem examinations were done on seven of the eight patients who died. No pathologic changes common to all were observed. In two cases (Cases 3 and 6)

there were extensive renal changes which were considered secondary to glomerular sclerosis. In Case 8 both kidneys showed almost complete fibrous replacement of the parenchyma together with lymphocytic infiltration. Hypotension and azotemia had developed in this patient after intravenous administration of only 4 gm. of terramycin. As pointed out, the serum level was 16 γ per milliliter 49 hours after the last dose in this case.

Penicillin Group.—Three patients (Cases 11, 12, and 13) received multiple intravascular injections of 12,000,000 units of penicillin (Table 2). In Case 11, an



Elevation of serum nonprotein nitrogen and blood urea nitrogen in parenteral terramycin therapy.

emaciated 64-year-old man had extensive metastases to the liver demonstrated at operation. Serum nonprotein nitrogen prior to penicillin therapy was 78 mg. per 100 ml. Three intravenous injections of 12,000,000 units of penicillin were given at four-hour intervals with no untoward effects. During the fourth injection the patient complained of a bad taste and died. At postmortem examination a primary bronchogenic epidermoid carcinoma with metastases to the liver and kidneys was found. No other cause of death was apparent.

In Case 12, a 52-year-old woman had previously had a pneumonectomy for carcinoma of the lung, roentgen therapy to the head and pelvis for pain, and electric shock therapy for a depression psychosis. On admission the patient was emaciated,

TABLE 2.—*Data on Patients Treated with Penicillin*

Patient	Age	Sex	Diagnosis	Non-protein Nitrogen	Date	Penicillin, 12,000,000 Units	Comment
11. S. T.	64	M	Epidermoid carcinoma of bronchus metastatic to liver and kidneys; exploratory laparotomy 8/28/51; severe back and chest pain; emaciation; massively enlarged, nodular, hard liver; BP 120/80	78	9/ 4/51	9/ 5/51 10 a. m. 9/ 5/51 2 p. m. 9/ 5/51 6 p. m. 9/ 5/51 11:30 p. m.	Mild pain at injection site No reaction No reaction Complained of taste, gasped, and died
12. C. C.	52	F	Carcinoma of lung, metastases to pleura, chest wall, breast, liver, adrenals, and kidney; pneumonectomy, irradiation to head and pelvis 1950; electric shock therapy 1951; emaciated, confused, evidence of peripheral thrombophlebitis	83	9/ 7/51	9/ 6/51 4 p. m. 9/ 6/51 8 p. m. 9/ 6/51 12 a. m.	No reaction No reaction Convulsive seizures after 8,000,000 units, followed by cyanosis, involuntary stool, and gradual recovery
13. E. T.	37	M	Carcinoma of tongue; hemiglossectomy Dec., 1950; cervical node removed May, 1951; radical neck dissection and resection of mandible 1951; increasing dysphagia, trismus, pain, bleeding, and confusion; large ulcerated defect in neck; BP 108/80	39	7/24/51	10/23/51 11 p. m. 10/24/51 7:15 a. m. 10/24/51 12:15 p. m.	No reaction No reaction Complained of "bad" taste; at completion of injection, gasped and died

confused, and tremulous. A mass was palpable in the left breast, and there was early gangrene of the tops of the fingers and toes of the left hand and foot. Two intravenous injections of 12,000,000 units of penicillin were given four hours apart with no untoward effects. During a third injection convulsive seizures developed and were followed by cyanosis and involuntary passage of stool. Antibiotic therapy was discontinued. The convulsions subsided, cyanosis disappeared, and the patient returned to her previous state. Death occurred nine days later; postmortem examination revealed tumor metastases to the pleura, chest wall, liver, adrenals, and kidneys.

A 37-year-old white man (Case 13) had a hemiglossectomy in 1950 and a radical neck dissection and resection of the mandible in 1951. On admission, he was confused and was considered to be in a terminal state. A large ulcerated defect in the side of the neck communicated with the buccal cavity. Two intravenous injections of 12,000,0000 units of penicillin were given four hours apart with no adverse effects. During the third injection the patient complained of a bad taste, and immediately after the injection he gasped twice and died.

In one case (Case 12) blood was obtained for determination of electrolyte and antibiotic levels before and after the first injection of penicillin. The data are given in Table 3. There was an insignificant decline in serum sodium and a slight rise

TABLE 3.—*Data from Case 12 on Electrolyte and Antibiotic Levels*

Time	Serum Na, mEq./L.	Serum K, mEq./L.	Serum Penicillin, Unit/Cc.
Control	158	3.85	10 units *
65 min	146	4.4	5,112 U
4 hr	149.5	4.3	1,278 U

* Patient had been receiving penicillin intramuscularly.

in serum potassium. Since the high level of penicillin had not decreased at the end of four hours, the assumption can be made that there was a subsequent stepwise increase in level with each injection.

In order to investigate the relationship of serum-penicillin level to the possible production of convulsions, a mongrel dog was given hourly intravenous injections for three hours of 3,000,000 units of penicillin G potassium dissolved in 30 cc. of distilled water. No effects were observed. A fourth injection of 6,000,000 units was then given; convulsions developed during the injection and the dog vomited and expired. Blood was drawn from a vein distant from the site of injection at approximately 5, 30, and 55 minutes after each injection for serum-penicillin determinations. The results are listed in Table 4. The stepwise increase in serum-penicillin concentration can be seen throughout the experiment.

COMMENT

In animals there appears to be an effect on renal function and blood pressure from terramycin, depending on dosage and rapidity of administration. A single subcutaneous injection of 400 mg. of terramycin hydrochloride per kilogram of body weight in rats was followed by prolonged diuresis.[10] No excretion of phenolsulfonphthalein was obtained one day prior to death in a dog given 225 mg. per

kilogram of terramycin sodium daily for six days.[10] Death on the 18th and 48th day, respectively, occurred in dogs receiving 150 and 75 mg. per kilogram of body weight daily; these animals had a decrease in excretion of phenolsulfonphthalein.

Slow intravenous injection of terramycin (100 mg. per kilogram given at the rate of 10 mg. a minute) did not cause any change in blood pressure in anesthetized dogs and cats.[10] A more rapid rate of injection caused a transient fall in blood pressure.[10]

In short experiments on human volunteers it was observed that, regardless of dose, the urinary excretion of terramycin was proportionately higher than after the injection of equal amounts of either aureomycin or chloramphenicol.[11] While urinary excretion of terramycin increased with increase in dose, doubling the dose did not double excretion. This observation suggests that there is a limit to the rate of excretion of this antibiotic even in the healthy subject.

TABLE 4.—*Relation of Penicillin Injections to Serum-Penicillin Levels in a Dog*

Penicillin Injected, Units	Time	Units Penicillin/Cc. Serum
3,000,000	0	.....
	5 min.	16
	40 min.	8
	55 min.	16
3,000,000	1 hr.	.....
	1 hr. 5 min.	256
	1 hr. 30 min.	256
	1 hr. 55 min.	1,024
3,000,000	2 hr.	.....
	2 hr. 5 min.	lost
	2 hr. 30 min.	4,096
	2 hr. 55 min.	4,096
6,000,000	3 hr.	Died during injection

It has been reported [4a] that rapid intravenous injection of 1 gm. of terramycin dissolved in 500 cc. of 5% dextrose three times daily for two or three days in human patients did not result in nephrotoxicity. Severe hypernatremia without exogenous dehydration was observed in five surgical patients given antibiotic agents which included terramycin [12]; the authors believed that there was no direct evidence of renal damage. The limited electrolyte studies done on two of the patients in the series herein reported showed no significant alteration in either serum-sodium or serum-potassium levels during therapy.

In a group of 91 patients treated with terramycin for pneumococcal and other types of pneumonia there were seven deaths.[5a] It is difficult to compare the course of these patients with those in our study, since therapy in the former group was mainly by the oral route. However, diarrhea and hypotension developed on the

10. P'an, S. Y.; Scaduto, L., and Cullen, M.: Pharmacology of Terramycin in Experimental Animals, Ann. New York Acad. Sc. **53**:238 (Sept. 15) 1950.

11. Welch, H.: Absorption, Excretion and Distribution of Terramycin, Ann. New York Acad. Sc. **53**:253 (Sept. 15) 1950.

12. Zimmerman, B., and Freier, E. F.: The Occurrence in Surgical Patients of Severe Hypernatremia Without Exogenous Dehydration, Surgery **31**:373 (March) 1952.

fifth day in one patient (Case 67) who received 1 gm. of terramycin intravenously daily. He died one day later; no serum nonprotein nitrogen determinations were made. Another patient (Case 73) became confused and died; postmortem examination showed bacteremia to have been controlled. A third patient (Case 88), who had chronic pyelonephritis in addition to pneumonia, had a serum-nonprotein-nitrogen level of 127 mg. per 100 ml. prior to death. The frequency with which nitrogen retention occurred was not known because repeated blood determinations were not made for most of these patients. Four patients in whom nitrogen retention was demonstrated all had severe vomiting and/or diarrhea. Two died with clinical evidence of uremia, and in the other two serum nonprotein nitrogen dropped rapidly and recovery ensued after administration of terramycin was stopped.[5a]

In a series of 112 patients with acute and chronic renal infections [5b] treated with orally administered terramycin (except for 2 who received the antibiotic intravenously) significant azotemia occurred in a few cases. Five patients with moderately elevated pretreatment blood-urea-nitrogen values had a marked rise during treatment. This was associated with severe nausea and vomiting in four of the patients; three of these patients died. In four additional patients the blood urea nitrogen rose markedly from normal values during treatment. The rise in one of these patients followed the appearance of uncontrollable nausea, vomiting, and diarrhea which persisted until death. The authors suggested that the nitrogen retention may have been caused or aggravated by the terramycin or, even more likely, by the nausea and vomiting which accompanied its administration. However, nausea and vomiting apparently were not present in all the patients who became azotemic. In our series nausea and vomiting were present in only one case; diarrhea did not occur.

In our patients the rapid terminal rise of serum nonprotein nitrogen was not accompanied by clinical jaundice and elevation of serum bilirubin comparable to that seen in certain patients treated with large parenterally administered doses of aureomycin.[3] Furthermore, the elevation of serum nonprotein nitrogen occurred more abruptly and was possibly less easily reversible than that observed after parenteral aureomycin therapy.

The studies of Sirota and Salzman [13] indicate that the renal excretion of aureomycin is solely a process of glomerular filtration of the component of that drug which is not bound to serum albumin. There is linear decrease in glomerular filtration rate as measured by average inulin clearance in persons beyond 30 years of age.[14] Reduced renal blood flow associated with severe chronic debilitating disease may produce renal insufficiency in the absence of kidney disease. If terramycin, an antibiotic so similar in many other ways, also resembles aureomycin in the manner of renal excretion, an impairment of glomerular filtration due to anatomical or functional causes will result in greatly delayed excretion and very high blood levels. The integrity of renal function appears to be a limiting factor in parenteral terramycin therapy, since badly damaged kidneys apparently excrete terramycin at a reduced rate. It is not unlikely that severe vomiting and diarrhea, which can

13. Sirota, J. H., and Salzman, A.: The Renal Clearance and Plasma Protein Binding of Aureomycin in Man, J. Pharmacol. & Exper. Therap. **100**:210 (Oct.) 1950.

14. Davies, D. F., and Shock, N. W.: Age Change in Glomerular Filtration Rate, Effective Renal Plasma Flow, and Tubular Excretory Capacity in Adult Males, J. Clin. Invest. **29**:496 (May) 1950.

occur with oral administration of terramycin, may be associated with dehydration and oliguria of sufficient magnitude to limit terramycin excretion and result in serum levels in a toxic range. This mounting level of terramycin then seems to produce an irreversibly pathologic state associated with azotemia. Intravascular retention of terramycin secondary to damaging renal disease in Case 8 may well have been the only precipitating cause of death. Although a total dose of only 4 gm. of terramycin had been given, a serum level of 16 γ per milliliter was still present 49 hours after the last dose of drug. Furthermore, despite a small total dose and discontinuance of therapy the degree of azotemia increased, shock developed, and death ensued.

The application of penicillin to the cerebral cortex of cats, dogs, monkeys, and human beings produces convulsions.[15] Within the concentrations used, the amount of penicillin appeared to be more important than its concentration. Such studies suggest that impaired renal function may result in penicillin plasma levels of such degree that cerebral irritation may follow.

Penicillin in an average daily dose of 86,000,000 units was given with no serious side-effects to a patient with bacterial endocarditis [4c]; 20,000,000 units of crystalline penicillin G potassium dissolved in 250 ml. of 5% glucose was administered every six hours. In order to determine the concentration reached during the daily dose of 80,000,000 units, a patient with normal renal function was given 20,000,000 units of crystalline penicillin G sodium in 250 ml. of physiologic sodium chloride solution intravenously every 6 hours for 24 hours. Samples of blood plasma obtained 10 minutes, 2 hours, 4 hours, and 6 hours after termination of the last infusion contained 1,050, 39.9, 8.4, and 2 units of penicillin.[4c] These levels are below those seen in our Case 12, in which convulsions developed. However, in this case and in Case 11 there was an elevated initial serum-nonprotein-nitrogen level. Cannon and associates [16] found that impaired renal function as shown by the Fishberg concentration test was associated with higher and more prolonged penicillin blood levels than would otherwise be anticipated.

It has been established that renal elimination of penicillin is by both glomerular filtration and tubular excretion.[17] The clearance of penicillin in man and dog approximates renal plasma flow at all plasma concentrations that have been studied.[18] Decreased renal plasma flow associated with advancing age [14] or chronic debilitating disease could be expected to produce higher serum-penicillin levels than would be seen in persons with normal renal function.

The growing realization that antibiotics should be employed in adequate dosage emphasizes the importance of establishing for the human patient the upper limits

15. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, J. A. M. A. **127**:217 (Jan. 27) 1945. Walker, A. E., and Johnson, H. C.: Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69 (Feb.) 1945.

16. Cannon, A. B.; Slatkin, M. H.; Chester, B., and Moses, R.: Penicillin Levels in Blood: Significance of Type of Preparation, Dosage, Kidney Function and Weight, J. A. M. A. **145**:1031 (April 7) 1951.

17. Beyer, K. H.; Miller, A. K.; Russo, H. F.; Patch, E. A., and Verwey, W. F.: The Inhibitory Effect of Caronamide on the Renal Elimination of Penicillin, Am. J. Physiol. **149**:355 (May) 1947.

18. Beyer, K. H.; Peters, L.; Woodward, R., and Verwey, W. F.: The Enhancement of the Physiological Economy of Penicillin in Dogs by the Simultaneous Administration of Para-Aminohippuric Acid, J. Pharmacol. & Exper. Therap. **82**:310 (Dec.) 1944.

of tolerance to these agents. That an antibiotic may have extremely toxic effects at certain dose levels in no way precludes its use at lower dose levels. However, when an infecting organism has been established as relatively resistant to certain antibiotics and high dose levels are required for its control, the toxic effects of the drug must be known. It may be necessary to change to an antibiotic with less toxic effect or to use a combination of antibiotics. Since different antibiotics exert toxic effects in different ways, such combinations at an effective total-dose level may be desirable in order to spread toxic effects.

Although the patients reported on were not treated primarily for infection (except in Case 8), the grave complications seen could be encountered in treatment of any disease state unless one wishes to make the unlikely assumption that the presence of infection has some protective effect on the patient. All our patients were seriously ill; however, the precise sequence of events observed has not been seen in similar patients under our observation who were not given such large doses of antibiotics.

SUMMARY AND CONCLUSIONS

Nine patients with far-advanced cancer and one patient with renal calculi and persistent urinary-tract infection were treated with parenterally administered terramycin. In eight cases there was rapidly progressive azotemia, followed by death. Marked hypotension was observed in the majority.

Three patients with far-advanced cancer received 12,000,000 units of penicillin intravenously every four hours. Sudden death occurred in two patients immediately after the third and fourth injections, respectively. In the third patient, convulsions developed during the third injection and were followed by recovery.

A correlation of studies done by others and the facts in these cases suggest that impaired renal function may slow excretion of terramycin and penicillin to such a degree that blood levels which are toxic to the patient ensue.

EFFECTS IN RHEUMATOID ARTHRITIS OF HYDROCORTISONE AND CORTISONE INJECTED INTRA-ARTICULARLY

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THE LOCAL action of cortisone [1] has been well demonstrated in the treatment of diseases of the eye.[2] Freyberg and co-workers [3] injected cortisone intra-articularly in eight patients with rheumatoid arthritis and observed temporary improvement in several. Hollander and associates [4] described the use of both cortisone and hydrocortisone locally in a group of patients with rheumatoid arthritis and other diseases. On the basis of clinical response and the change in intra-articular temperature on the day following injection of the hormone, they concluded that hydrocortisone was effective in suppressing inflammation and that cortisone was inactive in this respect.

In the present report are given the results obtained by serial intra-articular injections of cortisone and hydrocortisone in nine patients with rheumatoid arthritis and one patient with rheumatoid spondylitis with peripheral joint involvement. Seven of the patients had bilateral effusions in the knees, so that it was possible to obtain control observations between cortisone and hydrocortisone and the vehicle in which these drugs were suspended. Response to treatment was evaluated on the

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1. Cortisone as referred to in this article is compound E acetate and hydrocortisone is compound F acetate, formulated in a vehicle containing suspending agents and 0.9% benzyl alcohol. Hydrocortisone was supplied by Dr. Elmer Alpert, of Merck & Company, Rahway, N. J.

2. Leopold, I. H.; Purnell, J. E.; Cannon, E. J.; Steinmetz, C. G., and McDonald, P. R.: Local and Systemic Cortisone in Ocular Disease, Am. J. Ophth. **34**:361, 1951.

3. Freyberg, R. H.; Patterson, M.; Adams, C. H.; Durivage, J., and Traeger, C. H.: Practical Considerations of the Use of Cortisone and ACTH in Rheumatoid Arthritis, Ann. Rheumat. Dis. **10**:1, 1951.

4. Hollander, J. L.; Brown, E. M., Jr.; Jessar, R. A., and Brown, C. Y.: Hydrocortisone and Cortisone Injected into Arthritic Joints: Comparative Effects of and Use of Hydrocortisone as a Local Antiarthritic Agent, J. A. M. A. **147**:1629, 1951.

basis of objective changes in the injected joints and on the quantitative changes in the properties of the synovial fluid. The concentration of aminotripeptidase, an enzyme which has been observed in this laboratory to occur in the synovial fluid of patients with a variety of arthritides, proved to be a useful index of the extent of joint inflammation in the present investigation. I_t^t was used along with measurement of viscosity and leucocyte counts to evaluate the effects of therapy on the properties of the synovial fluid.

METHODS

Five patients were maintained on cortisone in well-stabilized dosage administered either orally or intramuscularly during the period of study. Before intra-articular injection of hormone, as much synovial fluid as could be aspirated was removed from the joint cavity. Ethyl chloride anesthesia was used, since procaine was observed to inhibit the aminotripeptidase of the synovial fluid. White and red cell counts were made on fresh fluid diluted twentyfold with isotonic sodium chloride solution. Relative viscosity was determined by using a single Ostwald viscosimeter in a bath at 38 C. either on fresh synovial fluid containing small amounts of heparin or on sterile clotted samples stored overnight in the refrigerator. Comparison between heparinized and sterile clotted samples showed no significant difference in the measured viscosity. Albumin-globulin ratios were determined on clotted samples of synovial fluid by the method of Albanese, Saur and Irby.[5] Aminotripeptidase content of the synovial fluid was determined by the method of Grassman and Heyde,[6] usually within several hours after aspiration, on unhemolyzed specimens centrifuged promptly after aspiration. The substrate was glycylglycylglycine;[7] 0.5 ml. of synovial fluid, 1.5 ml. of 0.02 M veronal buffer at pH 7.8, and 0.5 ml. of 0.25 M glycylglycylglycine solution, neutralized to pH 7.8, were incubated in a shaking water bath at 37 C. Two-tenths milliliter samples were removed from the reaction mixture at intervals and titrated with 0.015 N potassium hydroxide in 90% ethanol with 5 drops of thymolphthalein as indicator. Depending on the rate of hydrolysis, samples were removed at 30 to 90 minute intervals. A total of five titrations in duplicate were carried out in each determination. Results are given as percentage hydrolysis of glycylglycylglycine per hour. Repeated determinations showed no fall in tripeptidase activity of synovial fluid stored in the refrigerator over a period of weeks. When cortisone and hydrocortisone, suspended in vehicle, were added to the reaction mixture in final concentrations of 1 to 5 mg. per milliliter, no inhibition of enzyme activity was observed. Mucopolysaccharide concentration was determined by the method of Schloss.[8]

Before each injection the status of the involved joint was evaluated: The patient's subjective impressions were noted; the circumference was measured, and the degree of rest-pain, motion-pain, tenderness, heat, redness, and stiffness were scored from 1+ to 4+. After aspiration, the therapeutic agent—cortisone acetate (E) or hydrocortisone acetate (F) in a fixed dose of 25 mg. dissolved in 1 ml. of suspension vehicle—and the appropriate control—vehicle or, on three occasions, isotonic solution of sodium chloride—were injected into opposite knees. The agent injected is recorded in Tables 1 and 2 with the data of the subsequent joint aspiration, carried out three or four days later. Objective change in joint status is recorded as 0 to 4± (Table 1) according to whether the joint improved clinically or became worse.

RESULTS

Group I: Cases of Bilateral Knee Joint Involvement.—The treatment and course of three patients illustrative of varying degrees of improvement are summarized.

Case 1.—J. F. (Table 1, Fig. 1) had had rheumatoid arthritis for 3½ years and had been receiving cortisone therapy for 14 months. The dosage for the month preceding and the period

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6. Grassman, W., and Heyde, W.: Alkalimetrische Mikrobestimmung der Aminsäuren und Peptide, Ztschr. physiol. Chem. **183**:32, 1939.

7. Obtained from Hoffmann-LaRoche, Inc., Nutley, N. J.

8. Schloss, B.: Colorimetric Determination of Glucosamine, Analyt. Chem. **23**:1321, 1951.

of intra-articular therapy was uniformly maintained at 50 mg. a day by mouth. On this regimen, the patient had stiff, swollen knees with bilateral effusions. The right knee after 13 days of therapy, during which saline had been injected on two occasions, followed by two injections of cortisone, had worsened both symptomatically and objectively. The circumference had increased, the effusion remained large, and the tripeptidase activity (discussed hereafter) remained at

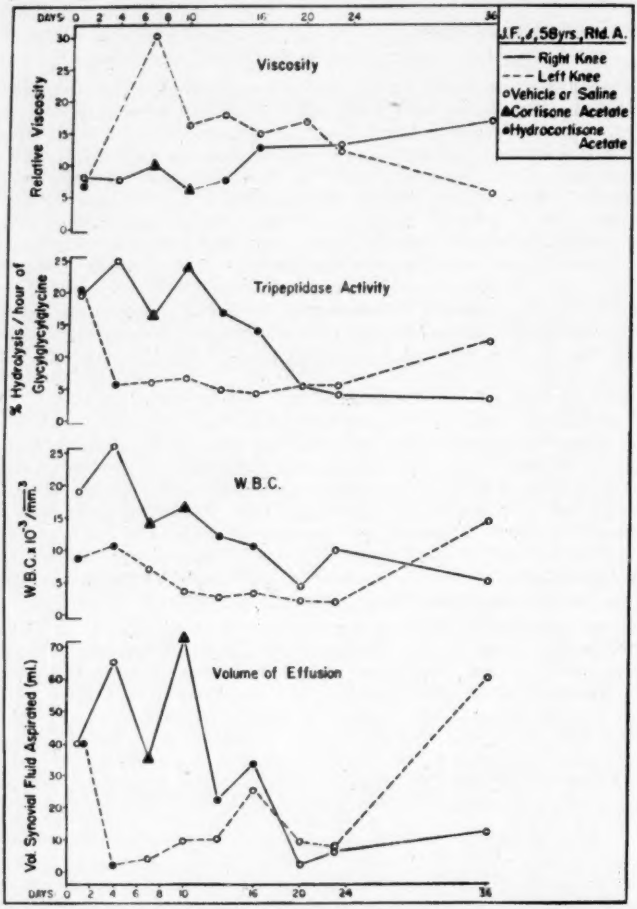

Fig. 1.—Effect of hydrocortisone acetate 25 mg., cortisone acetate 25 mg., and vehicle 1 ml. in a patient with rheumatoid arthritis and effusions in both knees (J. F., Case 1). On day 1 saline was injected instead of vehicle, and on days 20 and 23 nothing was injected. Insufficient fluid was obtained from the left knee on the fourth day for measurement of viscosity; 25 mg. of hydrocortisone was injected on that day.

approximately the pretreatment value. In contrast, one injection of hydrocortisone into the left knee had produced 4+ clinical improvement both symptomatically and objectively when the patient was seen three days later. There had been a marked decrease in the volume of the effusion and a fall in the tripeptidase level from 20.2 to 5.8%. After a second injection of hydrocortisone,

administered three days after the first, the clinical and laboratory improvement was maintained, and the viscosity rose from the pretreatment value of 13.8 to 30.3. The patient maintained striking clinical improvement in the left knee for 29 days following the first administration of hydrocortisone, during which time the cell count ranged between 1,800 and 3,500 and the tripeptidase level remained low. By the 36th day following the first injection, however, articular manifestations had worsened, a large effusion reappeared, and the cell count and tripeptidase level returned toward pretreatment values. A third injection of hydrocortisone at this time restored clinical improvement, which has persisted for three months.

A favorable effect on the right knee, in which, as was noted, cortisone had produced no improvement, was observed after one injection of hydrocortisone. This was manifested by 2+ symptomatic and 2+ objective change, though the properties of the synovial fluid showed

TABLE 1.—*Clinical and Synovial Fluid Changes Observed in Case 1 (J. F.)*

Day	Substance Administered in Preceding Injection*	Joint Change†		Joint Circumference		Volume Aspirated, Ml.	Relative Viscosity	W. B. C.	Diff.,‡ %	A/G Ratio	Tripeptidase % Hydrolysis/Hr.
		Symptomatic	Objective	In.	Cm.						
						Right Knee					
1	None	...	...	..	....	40	8.1	19,150	87-10-3	2.6/1.7	19.6
4	Saline, 1 ml.	—	—	16	40.6	65	7.7	26,000	85-10-5	3.4/2.0	25.2
7	V	—	—	16	40.6	35	9.9	14,100	80-4-10	2.8/1.8	16.6
10	E	—	=	17⅛	43.5	72	6.0	16,400	80-10-10	3.2/1.5	23.9
13	E	—	=	17⅛	43.5	22	7.5	12,000	.....	3.3/1.8	16.7
16	F	2+	2+	..	....	33	12.9	10,400	.....	3.1/1.3	14.1
20	F	3+	3+	16⅜	41.6	2	(Qns)	4,200	80-14-6	2.5/1.4	5.7
23	None	4+	3+	15½	39.4	6	12.9	9,860	.....	2.3/1.3	4.1
36	None	4+	2+	16	40.6	12	16.8	5,000	.....	2.1/1.4	3.5
93	V	1+	0	16⅜	42.5	85	7.2	14,000	75-22-2	3.1/2.6	15.9
98	E	2+	3+	16	40.6	71	10.3	8,900	62-38	.....	16.6
102	F	3+	3+	15½	39.4	16	170.0	6,000	48-52	2.5/2.0	5.6
165	X§	...	...	16	40.6	93	6.4	9,700	80-20	2.2/0.65	13.1
172	F	4+	4+	15½	39.4	6	over 1,000	5,000	3-97	2.0/0.89	5.3
						Left Knee					
1	None	...	...	..	....	40	6.6	8,900	90-8-2	1.7/1.9	20.2
4	F	4+	4+	15½	39.4	2	(Qns)	10,400	90-2-8	(Qns)	5.8
7	F	4+	4+	15	38.1	4	30.3	6,950	76-18-6	1.8/1.8	5.9
10	V	4+	4+	15⅝	39.7	9	16.3	3,500	90-5-5	3.0/1.2	6.9
13	V	4+	3+	15¼	38.7	10	18.0	2,400	.....	1.9/1.5	5.0
16	V	4+	3+	15½	39.4	25	14.9	3,200	.....	2.8/1.3	4.4
20	V	4+	3+	15⅝	39.7	9	16.8	1,800	95-5	2.6/1.3	5.6
23	None	4+	3+	15⅝	39	7	12.4	1,900	.....	2.3/1.3	5.3
36	None	—	—	16¼	41	50	5.5	14,250	.....	2.7/1.7	12.4

* V, vehicle, 1 ml.; F., 17-hydroxycorticosterone acetate (hydrocortisone), 25 mg.; E, 11-dehydro, 17-hydroxycorticosterone acetate (cortisone), 25 mg.

† Four plus, very marked improvement—complete or almost complete disappearance of effusion, swelling, warmth, tenderness, stiffness, and pain on motion when present; 3+, marked improvement—complete or almost complete disappearance of some but not all the signs; 2+, moderate improvement—reduction in several but not all signs present; 1+, slight improvement—reduction in a minority of signs present; 0, unchanged; —, worse—slight increase in several of signs present; =, worse—moderate increase in several of signs present.

‡ Values (%) are given in the order polymorphs, lymphocytes, other cells.

§ Hydrocortisone, 25 mg., was given on the 102d day.

only minor improvement. Four days after a second injection, however, the knee was almost asymptomatic, objective improvement was graded 3+ (only slight stiffness remained), the effusion was minimal, the synovial fluid cell count had decreased from a value of 12,000 before hydrocortisone to 4,200, and the tripeptidase activity had decreased from 16.6 to 5.7%. Improvement was maintained for 77 days, and then effusion and stiffness returned. Their return was accompanied by a fall in the viscosity of the synovial fluid from 16.8 to 7.2, a rise in cell count to 14,000, and an increase in peptidase level to 15.9%. A single injection of cortisone now was followed by significant clinical improvement, but the effusion remained large and the peptidase content of the synovial fluid was undiminished. A third injection of hydrocortisone was administered, improvement became more marked, viscosity increased sharply to 170, the leucocyte count

fell to 6,000, and the peptidase level decreased to 5.6%. After a fourth injection of hydrocortisone, the joint became completely symptom-free and improvement lasted for two months. A fifth injection of hydrocortisone then induced another remission, with a fall in cell count and tripeptidase and a rise in the viscosity of the synovial fluid to a value exceeding 1,000.

CASE 2.—B. E. (Table 2) had rheumatoid arthritis of 20 years' duration with advanced articular changes and many subcutaneous nodules. She had received no hormonal therapy before this study. Injection of cortisone into the right knee was followed by significant improvement clinically and in the properties of the joint fluid (Fig. 2). The amount of fluid decreased markedly and the tripeptidase content fell moderately. The viscosity remained unchanged. The effects of hydrocortisone subsequently injected into the opposite knee were more definite, however, with greater objective improvement (3+ after two injections) and more marked effects on the characteristics of the synovial fluid. Pain on motion and stiffness diminished,

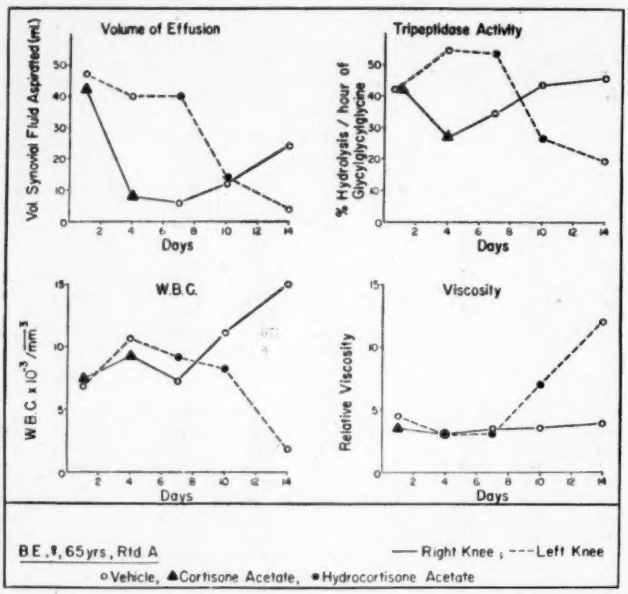

Fig. 2.—Effect of hydrocortisone acetate 25 mg., cortisone acetate 25 mg., and vehicle 1 ml. in a patient with rheumatoid arthritis (B. E., Case 2).

swelling subsided, the circumference was reduced from 13¾ to 12¾ inches (34.9 to 32.4 cm.), and the effusion disappeared. The cell count, tripeptidase activity, and volume of the synovial fluid fell, and the viscosity increased. There was reversal of the polymorph to round cell ratio of the synovial fluid (Table 2).

CASE 3.—E. S. had severe advanced rheumatoid arthritis of 13 years' duration. Marked clinical improvement was sustained for eight weeks with a dosage of 75 and 100 mg. of cortisone injected intramuscularly on alternate days. There were, however, persistent effusions in both knees with mild stiffness. The first and second intra-articular injections of hydrocortisone into the right knee produced only slight (+) objective improvement, which lasted three and seven days, respectively. Improvement consisted mainly of diminution in swelling. The circumference of the knee was reduced from 16 to 14¼ inches (40.6 to 36.2 cm.). There was an abrupt fall in the leucocyte count of the synovial fluid from 27,000 to 3,150 and in peptidase rate from 72.3 to 18.8%. The viscosity rose from 6.3 to 34.

In the left knee, cell count and tripeptidase level fluctuated widely when two successive injections of vehicle were given on days four and eight, and improvement was only 1+. Following a subsequent injection of cortisone, there was definite increase in joint pain and rise in leucocyte count from 2,050 to 19,000. Improvement in articular symptoms or synovial fluid was not observed after intra-articular cortisone injection. In this patient, although favorable changes in the synovial fluid were observed, clinical benefit from intra-articular injections of hydrocortisone was not great enough to warrant continuing them.

Group II: Cases of Asymmetrical Joint Involvement.—Three patients with rheumatoid arthritis received intra-articular injections of hydrocortisone into single joints without controlled observations in opposite joints. Examination of synovial fluid from these patients was not done.

CASE 4.—J. M., a 47-year-old man receiving no specific therapy, had had for six weeks a markedly (4+) swollen, extremely tender, warm, and painful elbow. The joint was fixed at 110 degrees. Hydrocortisone, 25 mg., was injected intra-articularly. By the following day mobility had increased, and on the third day the range of motion was 50 degrees, pain was absent, and

TABLE 2.—*Clinical and Synovial Fluid Changes Observed in Case 2 (B. E.)*

Day	Substance Administered in Preceding Injection	Joint Change		Joint Circumference		Volume Aspirated, Ml.	Relative Viscosity	W. B. C.	Diff., %	A/G Ratio	Tripeptidase % Hydrolysis/Hr.
		Symptomatic	Objective	In.	Cm.						
						Right Knee					
1	None	...	...	14	35.5	42	3.5	7,400	82-18	2.4/1.9	41.2
4	E	1+	2+	13½	34.3	8	3.1	9,250	68-32	2.1/1.5	26.9
7	E	2+	2+	13½	34.3	6	3.4	7,250	60-30	2.8/1.5	34.6
10	V	2+	1+	14	35.5	12	3.6	11,150	70-30	2.2/1.2	43.8
14	V	2+	1+	13¾	34.9	24	3.9	15,000	80-16	1.8/1.2	45.9
						Left Knee					
1	None	...	...	13½	34.3	47	4.5	6,800	64-36	1.9/1.5	41.8
4	V	±	±	13½	34.3	40	3.2	10,650	92-8	3.6/1.6	54.7
7	V	±	0	13¾	34.9	40	3.3	9,150	61-29	3.4/1.4	53.7
10	F	1+	2+	13¾	33.6	14	7.1	8,250	56-30-4	2.4/1.2	26.6
14	F	2+	3+	12¾	32.4	4	12.1	1,800	20-80	2.3/1.2	19.4

only slight heat, moderate tenderness, and moderate swelling were noted. On the seventh day the range of motion was 120 degrees, and slight tenderness and swelling remained. Improvement was maintained for 15 days, after which a gradual relapse began in spite of the fact that daily intravenous injections of corticotropin (ACTH) (20 mg. in 24 hours) had been started on the 12th day. When hydrocortisone was again injected, twice in a five-day period, a similar course of events occurred; marked improvement was induced for seven days and was followed by a partial relapse. Significant improvement was maintained for 22 days. Another injection of hydrocortisone at this time was followed by marked improvement for 14 days.

CASE 5.—F. G., a 28-year-old man receiving no specific therapy, had a markedly swollen (3+), painful, warm, and tender elbow. The condition had persisted for over a year. Flexion was limited to 90 degrees. Hydrocortisone, 25 mg., was injected intra-articularly after aspiration of a few drops of synovial fluid. Improvement began a half-hour after injection. When the patient was seen three days later, there was no heat or pain and stiffness was minimal. The range of flexion had increased to 115 degrees. Improvement was maintained for eight days.

CASE 6.—L. G., a 58-year-old woman with advanced rheumatoid arthritis, had a chronically stiff, painful, and tender knee which made rising and walking difficult. There was no effusion. Three days after one intra-articular injection of 25 mg. of hydrocortisone, there was a significant though small decrease in pain and tenderness. Hydrocortisone was again injected, and this was followed by marked improvement. The joint circumference decreased from 14⅝ to 14¼ inches (37.2 to 36.2 cm.) in three days, and there was only residual mild stiffness.

Symptomatic improvement continued undiminished when the patient was seen repeatedly over a 37-day period. Objectively, however, stiffness and pain on motion, which reappeared gradually, had returned almost completely by the 37th day.

COMMENT

Several sources of error may be encountered in evaluating the local effect of compounds introduced into joints of patients with rheumatoid arthritis. The severity of the arthritis may spontaneously fluctuate; symmetrical joints observed for comparison may be unequally affected; the hormone injected locally may be absorbed and then exercise a systemic effect; cortisone given systemically at the same time that cortisone or hydrocortisone is injected locally may contribute to the local improvement observed. Attempts have been made to correct for each of these factors. Bilateral joints were observed simultaneously; into one hydrocortisone or cortisone was injected and into the other vehicle. Improvement to a significantly greater degree observed consistently in the hydrocortisone-treated joint as compared with the control joint or other affected joints renders untenable the possibility that the simultaneous administration of cortisone orally or intramuscularly may have been responsible for the observed result. Similarly, correction for the possibility of spontaneous improvement in the treated joint was made by controlled studies of symmetrically affected joints at intervals of several days. When the knee joints were affected to an unequal degree, hydrocortisone was injected into the joint more severely involved. The frequent occurrence of improvement in one knee locally treated with hydrocortisone in the face of worsening of the opposite joint into which vehicle was simultaneously injected is evidence against the possibility of constitutional effects resulting from the absorption of locally injected cortisone. Finally, improvement in the treated joint lasted an average of seven days, a much longer period than one would expect from the systemic effect of a single injection of 25 mg. of hydrocortisone.

Aminotripeptidase is an enzyme which is present in many types of cells [9] and is found in especially high concentration in leucocytes. We have observed the regular occurrence of this enzyme in the synovial fluid from patients with a variety of arthritides [10] and have found it to be present in relatively high concentration, up to 18 times the serum level, in the synovial fluid of patients with rheumatoid arthritis and in low concentration in degenerative joint disease and traumatic arthritis. Changes in the level of aminotripeptidase have been consistent with changes in the clinical appearance of the joint and cell count and viscosity of the synovial fluid. The level of tripeptidase in synovial fluid may be presumed to be related to the amount of cellular degeneration in the synovial fluid and the surrounding tissue and in this way may serve as an index of the intensity and extent of the synovial inflammatory reaction. Further observations concerning its concentration in synovial fluid will be published elsewhere.[10]

The data presented support the conclusion of Hollander and his associates [4] that hydrocortisone is effective locally in suppressing the synovial inflammation of rheumatoid arthritis. This effect was well demonstrated in J. F. (Table 1), who

9. Ellis, D., and Fruton, J. S.: On the Proteolytic Enzymes of Animal Tissues: IX. Calf Thymus Peptidase, J. Biol. Chem. **191**:153, 1951.

10. Ziff, M.; Simson, J.; Ford, D. K.; Smith, A., and Bunim, J. J.: Unpublished data.

showed prolonged periods of improvement associated with decrease in the volume of effusions, rise in synovial fluid viscosity, and fall in cell count and tripeptidase content of the synovial fluid. Improvement was noted within a day after injection of the hormone. Remissions lasting from 30 days to 3 months were induced in each knee. Cortisone, on the other hand, did not induce improvement in joint status after two intra-articular injections; the effusion remained large and there was no significant improvement in the properties of the synovial fluid (days 10 and 13, left knee, Table 1). On one occasion (right knee, day 98), cortisone treatment was followed by objective improvement of considerable extent, but the effusion volume remained large and peptidase level elevated. During a six-month period, hydrocortisone was injected into this patient's right knee at intervals as required, and as a result it was possible gradually to discontinue his oral cortisone therapy. In the other nine patients, less striking but definite and consistent improvement was noted both clinically and in the properties of the synovial fluid after hydrocortisone injection.

TABLE 3.—*Effect of Cortisone and Hydrocortisone on Clinical Status of Knee Joints and Properties of Synovial Fluid in Seven Patients with Bilateral Effusions*

Substance Injected*	No. of Injections	% Showing 2+ Objective Improvement or Better	% Showing Significant Improvement in Synovial Fluid
Cortisone	13	31	23
Hydrocortisone	20	80	95
Vehicle†	22	0	14

* Steroid 25 mg. and vehicle 1 ml.
† In 3 instances isotonic solution of sodium chloride was used. Patient is not listed if improvement continued after previous injection of hydrocortisone.

Table 3 is a summary of the effects of cortisone, hydrocortisone, and vehicle in a group of seven patients with bilateral effusion. Eighty per cent of injections with hydrocortisone were followed by at least 2+ objective improvement and 95% by significant changes toward normal in the properties of the synovial fluid. The results obtained with cortisone were less favorable; 31% of the injections were followed by clinical improvement and 23% by improvement in the characteristics of the synovial fluid. In 31%, however, injection of cortisone was followed by accentuation of joint symptoms and an increase in the abnormal attributes of synovial fluid.

Clinical improvement after intra-articular therapy began usually on the day following injection of hydrocortisone but often within three hours. Though prolonged periods of improvement were induced in three patients, J. F. (Case 1), L. G. (Case 6), and M. F. (the last not described in this article), lasting from 27 to 90 days, the duration of improvement in the other patients averaged 8 days and varied from 4 to 15 days.

The distinct superiority of hydrocortisone over cortisone in establishing improvement in joint status and synovial fluid suggests that the former or a metabolic product of it may be the active substance that induces the suppression of tissue reaction. This would imply that cortisone, when given systemically, is reduced either to hydrocortisone or another active steroid at least in quantities sufficient to exert a therapeutic effect. The lack of significant local action on the part of cortisone,

in the doses used, suggests that this reduction to a biologically active metabolite does not occur to a significant extent in synovial tissue. The distinct local therapeutic effects of cortisone in the eye may result from relatively greater local concentration or from the fact that corneal or conjunctival epithelium in contrast to synovial tissue may possess the capacity to convert cortisone to an active agent.

Increase in relative viscosity of the synovial fluid coincided fairly consistently with clinical improvement and with other favorable changes in the synovial fluid, such as decrease in cell count and tripeptidase content. On two occasions (Table 1) there were sharp increases in viscosity after injections of hydrocortisone to values of 170 and above 1,000, respectively. Giansiracusa, Ropes, Kulka, and Bauer [11] have noted a marked and progressive rise in the viscosity of the synovial fluid in the course of administration of adrenocorticotropic hormone intramuscularly to a patient with rheumatoid arthritis. Ragan and Meyer [12] on the basis of comparison of the viscosity and mucopolysaccharide concentration of synovial fluid concluded that the hyaluronic acid of the synovial fluid of rheumatoid arthritis is in a relatively depolymerized state. An increase in viscosity of synovial fluid following hydrocortisone given locally or corticotropin (ACTH) administered systemically would suggest

TABLE 4.—*Effect of Intra-Articular Injection of Hydrocortisone Acetate on Viscosity of Synovial Fluid**

Treatment	Glucosamine Concentration (Mg./Ml.)	Relative Viscosity
Before intra-articular injection of hydrocortisone	1.27	6.4
3 days after intra-articular injection of hydrocortisone	1.63	>1,000

* Patient J. F., days 165 and 172 (Table 1); 25 mg. of hydrocortisone was injected.

that improvement in the arthritic process is associated with reversion of the hyaluronic acid of synovial fluid to a more highly polymerized state. That increase in the concentration of mucopolysaccharide in the synovial fluid, as reflected by glucosamine concentration, is not responsible for the rise in viscosity is demonstrated in Table 4. It is not possible at present to decide whether the rise in viscosity observed is secondary to suppression of synovial inflammation or is the result of an independent effect of hydrocortisone on the state of polymerization of hyaluronate in synovial fluid.

The proteins of the synovial fluid are believed to enter the synovial cavity by diffusion from the synovial capillaries.[13] The presence of an inflammatory reaction in the synovial membrane could conceivably increase the protein content of the synovial fluid through an increase in rate of cellular disintegration and also by interference with lymphatic absorption of protein. Since both capillary permeability [14]

11. Giansiracusa, J. E.; Ropes, M. W.; Kulka, J. P., and Bauer, W.: The Natural Course of Rheumatoid Arthritis and the Changes Induced by ACTH, Am. J. Med. **10**:419, 1951.

12. Ragan, C., and Meyer, K.: The Hyaluronic Acid of Synovial Fluid in Rheumatoid Arthritis, J. Clin. Invest. **28**:56, 1949.

13. Bauer, W.; Ropes, M. W., and Waine, H.: The Physiology of Articular Structures, Physiol. Rev. **20**:272, 1940.

14. Robson, H. N., and Duthie, J. J. R.: Capillary Resistance and Adrenocortical Activity, Brit. M. J. **2**:971, 1950.

and inflammation are reported to be diminished by cortisone, one might expect the protein content of the synovial fluid to be influenced by intra-articular therapy. Our data, however, have shown no consistent effects on either total protein content or albumin-globulin ratio.

Intra-articular therapy in rheumatoid arthritis is indicated in patients in whom one or two joints are involved. It may also be employed to advantage in cases in which corticotropin (ACTH) or systemic cortisone therapy in relatively low dosage achieves satisfactory effect in all but one or two joints. Rather than raise the daily dose in order to affect the more resistant joints, it may be desirable to retain the lower dosage schedule and supplement it with periodic intra-articular injections of hydrocortisone.

Intra-articular therapy was discontinued in seven cases. Two of the patients, who were subsequently given cortisone orally because they had generalized disease, did well enough on systemic therapy to make intra-articular treatment unnecessary. A third patient had a moderate remission in the locally treated joint, but a severe exacerbation developed in numerous other joints, removing the indication for local treatment. In a fourth patient improvement was not sufficient to warrant further treatment, and in two patients the discomfort of aspiration rendered intra-articular therapy undesirable. One patient had a satisfactory remission, and three derived sufficient benefit from intra-articular therapy to warrant and to accept repeated injections of hydrocortisone. In the latter, duration of improvement lasted from two weeks to several months after either one or two injections.

The purposes of the present article are to present data indicating that hydrocortisone is active locally and that cortisone is relatively inactive in this respect and also to describe the quantitative changes observed in the synovial fluid. Though it is evident from our results here reported that hydrocortisone has a local suppressive action on joint inflammation, definite conclusions concerning its utility as a practical therapeutic procedure will have to await a more prolonged trial in a larger group of patients. It will be necessary in this connection to evaluate first the acceptability to the patient of a procedure which requires, in the majority of instances, repeated joint injections at approximately weekly intervals for an indefinite period and secondly the progression of the underlying disease in the treated joint.

SUMMARY

1. Nine patients with rheumatoid arthritis and one with rheumatoid spondylitis received intra-articular therapy with hydrocortisone. Seven of these had bilateral effusions in the knee joints, permitting comparison of the effects of intra-articular injections of hydrocortisone, cortisone, and suspending vehicle in the same patient.

2. Of hydrocortisone injections (25 mg.), 80% were followed by 2+ objective improvement or better when the patient was examined three days later; 95 per cent of injections were followed by significant improvement in the properties of the synovial fluid. Only 31% of cortisone injections (25 mg.) were followed by similar improvement clinically, and 23% by improvement in the properties of the synovial fluid. There were no instances of 2+ objective clinical improvement after injection of suspending vehicle, and only 14% of injections were followed by significant improvement in the synovial fluid.

3. Periods of improvement lasting from 27 to 90 days were induced in three patients by intra-articular injection of hydrocortisone; the duration of improvement in the other patients averaged 8 days and varied from 4 to 15 days.

4. The most consistent changes in the synovial fluid after intra-articular injection of hydrocortisone were a rise in viscosity and a fall in aminotripeptidase content. These changes were accompanied by a fall in the leucocyte count and an increase in the percentage of lymphocytes. Total protein and albumin-globulin ratios were not consistently altered.

5. The aminotripeptidase content of the synovial fluid appeared to be a useful index to the degree of synovial inflammation.

6. Marked increase in relative viscosity of the synovial fluid was associated with relatively small change in glucosamine concentration, suggesting that the rise in viscosity following intra-articular hydrocortisone is due to an increase in the state of polmerization of synovial hyaluronate.

7. Intra-articular therapy found continued utility in the treatment of 4 of 10 patients. The therapeutic usefulness of this procedure on a long term basis remains to be evaluated.

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THERAPEUTIC TRIALS OF RADIOGALLIUM (Ga^{72})

A Report of Four Cases

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RESULTS of studies of the distribution of gallium and its excretion pattern and toxicity in experimental animals have been reported by Dudley and associates [1] and by King and others.[2] Clinical trials in the radioactive use of the isotope Ga^{72} as a possible diagnostic agent for the early localization of malignancies involving bone have been reported by Mulry and Dudley [3] and by King and associates.[2c] Brucer and associates [4] have reported upon the results of a therapeutic trial of Ga^{72}.

Radiogallium, $_{31}GA^{72}$, is produced by neutron bombardment of natural gallium (Ga^{69}, Ga^{71}) with thermal neutrons, resulting in a mixture of radioactive gallium (Ga^{70} and Ga^{72}). Ga^{70} has a half life of 20 minutes and plays no important biological role. Ga^{72} has a half life of 14.3 hours and is a beta and gamma emitter. The mean effective beta energy equals 0.45 mev, while the gamma emission is 1.59 times as energetic as the gamma emission of a similar quantity (millicurie) of radium. The

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1. (*a*) Dudley, H. C.: Determination of Gallium in Biological Materials, J. Pharmacol. & Exper. Therap. **95**:482-486, 1949. (*b*) Dudley, H. C.; Munn, J. I., and Henry, K. E.: Studies of the Metabolism of Gallium, ibid. **98**:105-110, 1950. (*c*) Dudley, H. C.; Henry, K. E., and Lindsley, B. F.: Studies of the Toxic Action of Gallium, ibid. **98**:409-417, 1950. (*d*) Dudley, H. C.: Gallium Citrate and Radiogallium (Ga^{72}) Citrate, J. Am. Chem. Soc. **72**:3822—3823, 1950. (*e*) Dudley, H. C.; Imirie, G. W., Jr., and Istock, J. T.: Deposition of Radiogallium (Ga^{72}) in Proliferating Tissues, Radiology **55**:571-578, 1950. (*f*) Munn, J. I.; Walters, N. H., and Dudley, H. C.: Urinary Excretion of Gallium by Man and Animals, J. Lab. & Clin. Med. **37**:676-682, 1951.

2. (*a*) King, E. R., and Perkinson, J. D.: Preliminary Distribution Studies of $_{31}Ga^{72}$ in the Wistar Rat, Texas Rep. Biol. & Med. **8**:491-497, 1950. (*b*) King, E. R.; Perkinson, J. D., Jr.; Bruner, H. D., and Gray, J.: Excretion of Gallium by the Rat and by Man, Science **113**:555-557, 1951. (*c*) King, E. R.; Mason, M. W.; Messinger, H. B., and Dudley, H. C.: Preliminary Report on the Use of Ga^{72} in Clinical Tracer Studies, Radiology, to be published.

3. Mulry, W. C., and Dudley, H. C.: Studies of Radiogallium as a Diagnostic Agent in Bone Tumors, J. Lab. & Clin. Med. **37**:239-252, 1951.

4. Brucer, M., and others: Therapeutic Use of Ga^{72}, Radiology, to be published.

tissue dose (beta and gamma) for human beings is approximately 85 r per millicurie per gram of tissue for total disintegration.

Gallium has been shown to be deposited at a rather rapid rate in areas having osteoblastic activity, such as the epiphysis in young animals, healing fractures, osteogenic sarcomas, and certain metastatic lesions involving bone.[5] Gallium was found to be moderately toxic; on a basis of 1 mg. of gallium per kilogram of body weight, the toxic effects were more pronounced on larger animals than on smaller species.[1c] In experimental animals, the limiting condition for the study of the radiation effects of Ga^{72} is the toxicity of the carrier gallium.

Radiogallium (Ga^{72}) citrate in tracer amounts (300 to 800 mc.) has been used clinically for study of its localization in malignant bone lesions by means of externally positioned Geiger tubes.[6] The findings indicated that gallium is concentrated in some metastatic lesions of the osteoblastic type. Its usefulness as a diagnostic agent is still being studied.

A study of 21 patients treated with a therapeutic course of radiogallium (Ga^{72}) citrate has been reported. The results indicated that in order to approximate the tissue level of radiation necessary for cancericidal effect, a toxic dose of the carrier gallium was necessary. Consequently, use of Ga^{72} was considered ineffective as a therapeutic measure in this series of cases.[4]

This report presents the clinical, x-ray, and autopsy findings on four patients treated with repeated doses of radiogallium (Ga^{72}) citrate. There was one case of carcinoma of the urinary bladder, one case of carcinoma of the prostate, one case of carcinoma of the breast, and one case of malignant synovioma, all with metastases to bone.

MATERIAL AND METHODS

Radiogallium citrate was prepared as described previously[1d]; 1 ml. of gallium solution contained approximately 1 mc. of Ga^{72} and 6 mg. of stable gallium, at pH 6.5, with an excess of citrate ions. Prior to administration, the patient received intravenously 500 mg. of calcium chloride in aqueous solution to prevent tetany due to the excess citrate which would immobilize the blood calcium. The radioactive solution was administered intravenously by means of a gravity-flow arrangement such that the flask tubes and needle were flushed with isotonic sodium chloride solution.

Patients thus treated were isolated but were not placed in shielded rooms. At no time was there more than one patient receiving Ga^{72} in one ward. None of the patients required special nurses; consequently routine nursing procedures were adequate in all cases.

No special diets or drugs were necessary because of the gallium therapy. All the urine was collected at 24-hour intervals for 96 hours after injection, and the retention of gallium was estimated by radioassay performed on the urine specimens.

REPORT OF CASES

Case 1.—A 61-year-old white man, a pharmacist, was admitted to this hospital April 18, 1950, with a diagnosis of transitional cell carcinoma of the bladder, which had been fulgurated on several previous occasions. In July he had x-ray therapy to the pelvis with good palliative effect. A Ga^{72} tracer study done June 5 revealed areas of increased uptake over the eighth and ninth thoracic vertebrae, the second and third lumbar vertebrae, the pelvis bilaterally, and the proximal ends of both femurs. As a palliative measure, 269 mc. of Ga^{72} was given from Aug. 20 through Jan. 8, 1951.

5. Dudley.[1a] Dudley, Imirie, and Istock.[1e]

6. King, Mason, Messinger, and Dudley.[2c] Mulry and Dudley.[3]

This patient, although negativistic toward any therapy, improved to the extent that an indwelling catheter required for several months was removed. Afterward he could void ad libitum. Two weeks after the therapeutic course was complete, he was able to be up and about in a wheel chair, although previously he had been bedridden.

X-ray examinations showed osteolytic lesions in the pelvis and lumbar spine throughout and after the course of Ga^{72}. The patient died March 22. The autopsy pathological diagnosis was transitional cell carcinoma of the bladder, with metastases to the prostate; seminal vesicles; regional lymph nodes; pleura and lungs bilaterally; preaortic lymph nodes; 4th, 5th, 8th, 9th and 11th thoracic vertebrae; 1st, 2d, and 3d lumbar vertebrae; 4th and 5th ribs on the left; right 5th rib; right and left ilium, and right femur.

CASE 2.—E. R., a 61-year-old white man, a metal worker, was first admitted to this hospital in November, 1947, at which time the diagnosis of Paget's disease and carcinoma of the prostate with metastases to the pelvis was made. He had previously undergone a prostatectomy for adenocarcinoma of the prostate. A bilateral orchiectomy was performed, and administration of diethystilbestrol was started. Because of the progressive nature of the pain, he was given x-ray therapy to the pelvis, but without relief. A Ga^{72} tracer study in March, 1950, revealed increased uptake over the metastatic lesions in the right pelvis. In April and May, he was treated with 26.5 mc., in July he received 9 mc., and from Oct. 16 through Dec. 18 he received 150 mc. of Ga^{72}.

This patient, after the first and second single-dose therapies, reported marked relief of bone pain and was able to walk about more easily. After the intensive therapeutic course given late in 1950, the patient again claimed a reduction of bone pain. The patient's attitude tended toward euphoria, and this made it doubly difficult to evaluate his improvement.

X-ray examinations demonstrated a large dense osteoblastic mass in the right ilium. Two months after Ga^{72} therapy, the center of the sclerotic lesion appeared less dense by x-ray. Whether or not this was a result of gallium therapy is debatable.

In February, 1951, the patient was admitted to the Medical Division of the Oak Ridge Institute of Nuclear Studies in Oak Ridge, Tenn., and died on April 26. During this hospitalization period he received 441 mc. of Ga^{72}. At autopsy there was a large, irregular, nodular, cystic lesion in the pelvis invading the ilium and pubic bones on the right and extending to the midline. The pubic bones on both sides were invaded with tumor. Histologically, the lesion was an adenocarcinoma of the prostate.

CASE 3.—W. B., a 29-year-old white woman, had a left radical mastectomy for adenocarcinoma of the breast in April, 1950. Because of rapid metastatic growth, a bilateral oophorectomy was performed in June; two courses of x-ray therapy were given in June, 1950, and January, 1951, and two courses of Ga^{72} were administered in March and July of 1951. The first Ga^{72} therapy was 317 mc. given over a period of 30 days. This was followed by subjective alleviation of bone pain. The second course was 190 mc. given over a period of 15 days. The first Ga^{72} tracer study, in March, 1951, revealed no areas of increased uptake, but the second tracer study, in July, 1951, revealed areas of increased uptake over the upper and lower right ilium posteriorly. The patient was extremely cooperative and felt she received marked benefit from the first course of Ga^{72} therapy. In the four-month interval between therapies, she showed x-ray evidence of bone healing of the inferior ramus of the right pubis, the right scapula, and possibly the first lumbar vertebra. Death occurred on Sept. 16. There was no local recurrence at the mastectomy site. Histologically, the tumor was a poorly differentiated adenocarcinoma with metastases to abdominal lymph nodes, diaphragm, liver, bone, pleura, and lungs.

CASE 4.—S. B., a 28-year-old Negro man, a teacher, was admitted to this hospital on June 11, 1951, where the diagnosis of synovial sarcoma of the right elbow with possible metastases to the fifth cervical vertebra was made. On June 21 a right mid-arm amputation was performed, with the removal of two axillary lymph nodes. Because of the onset of severe pain in the right shoulder and neck and the x-ray evidence of destruction of the body of the fifth cervical vertebra, the patient was given a course of Ga^{72}, 73 mc. over a 14-day period (from Aug. 23 to Sept. 6). Because severe nausea developed, the Ga^{72} therapy was discontinued. The pathological diagnosis was synovial sarcoma, right arm. The patient claimed no beneficial effect from Ga^{72} therapy. Repeated x-ray examinations showed progressive osteolytic metastases throughout his hospital stay.

Details of Administration of Radioactive Gallium (Ga^{72})

Case No.	Age, Yr.	Sex	Diagnosis *	Radiogallium Administered (Mc.†)	Stable Gallium Administered ‡ (Mg.)	Estimated Stable Gallium Retained (Mg.§)	Areas of Bone Destruction Shown by X-ray Examination	Laboratory Studies	
								Pretherapy	Post-Therapy
1	62	M	Transitional cell carcinoma of urinary bladder with bone metastases (A, B, C, X)	Single dose 8/20/50, 11.0 10/ 9/50, 22.3 11/ 3/50, 23.5	300	137	3d lumbar vertebra (1950), 11th and 12th thoracic vertebrae (8/17/50), L. ilium (12/2/50), upper ends of both femurs (2/20/51)	WBC 6700 (6/16/50)	WBC 3400 (1/11/51)
				Therapeu. course of 6 weekly injections 12/4/50-1/8/51 Total 212 mc.	1,080	644			
2	61	M	Carcinoma of the prostate with bone metastases (A, B, C, X)	Single dose 4/24/50, 14.0 5/22/50, 12.3 7/24/50, 9.2 10/16/50, 24.1	690	513	Lower ½ R. ilium, R. and L. pubis, R. and L. ischium, shaft of R. femur (3/20/50)	WBC 9400 (3/31/50) Acid phosphatase 17.6 Alkaline phosphatase 11.6 (3/21/50)	WBC 8300 (12/15/50)
				Therapeu. course of 6 weekly injections 11/13/50-12/18/50 Total 126 mc.	720	455			
3	29	F	Carcinoma of breast with generalized bone metastases (A, B, C, X)	Therapeu. course of 8 semiweekly injections 3/12/51-4/16/51 Total 317 mc.	1,920	453	R. scapula, 1st lumbar vertebra, medial ½ of R. ilium, R. and L. acetabulum, inferior ramus of R. pubis and L. pubis (3/15/51)	WBC 6700 (3/8/51)	WBC 1625 (6/22/51) WBC 800 (8/24/51)
				Therapeu. course of 5 semiweekly injections 7/30/51-8/13/51 Total 190 mc.	880	528			
4	28	M	Malignant synovioma with bone metastases (B, C, X)	Therapeu. course of 4 weekly injections 8/23/51-9/13/51 Total 121 mc.	720	204	5th cervical vertebra, upper end and shaft of R. humerus (8/8/51)	WBC 13,000 (6/13/51)	WBC 6800 (9/15/51)

* Diagnosis based on: (A) autopsy findings; (B) biopsy; (C) clinical impression; (X) x-ray findings.
† Effective half life of Ga^{72} in man is approximately 12 hr.
‡ This is the nonradioactive gallium which accompanies the Ga^{72}.
§ Estimated by study of the 0-48 hr. urinary excretion of Ga^{72}.

COMMENT

The four patients reported on had incurable malignant conditions, the diagnoses of which were verified by surgical biopsy and autopsy. There were no possible therapeutic measures remaining for any of these patients.

From data which have been presented, three of the four patients given test therapy doses of Ga^{72} appeared clinically and/or subjectively to have received some benefit. Their lesions were so widespread that it would have been impossible to treat all bone metastases with palliative x-ray therapy. From previous experience, the relief of bone pain was in no case greater in these patients than in patients treated with x-rays. It is realized that subjective clinical findings cannot be depended upon to any great extent in the evaluation of a new drug.

In two patients there was continued progression of the bone lesions, as discerned by x-rays, throughout and after the course of therapy. One patient showed a decrease in density of a previous large sclerotic lesion of the ilium. This change in x-ray appearance has been known to occur in similar patients receiving no therapy. One patient had roentgenographic evidence of an increase in density of some lesions which might be attributed to an attempt at healing.

It was necessary to terminate Ga^{72} therapy in one case because of a marked leucopenia. In Case 3, the white blood cells dropped to 500, terminating the first course, and to about the same level during the second course.

Patient 1 had a dry, scaly erythematous rash about two weeks after the completion of his therapeutic course. Patient 3 complained of the same symptoms after a similar interval. Patients 1, 3, and 4 had severe nausea and vomiting after four or five injections (a total of about 500 mg. of stable gallium). Patient 4 had severe nausea and vomiting after the third and fourth injections, necessitating termination of the course.

Autopsy findings on the three patients who died substantiated the diagnosis but were not impressive in regard to beneficial results from Ga^{72} therapy. The results indicate that a toxic dose of carrier stable gallium is administered before it is possible to deliver an adequate dose of radiation to the bone lesions. This limiting factor of stable-gallium toxicity eliminated the use of Ga^{72} as a therapeutic agent under present methods of preparation and administration.

SUMMARY

The clinical courses of therapeutic trials of radiogallium (Ga^{72}) in four cases of incurable bone cancer have been presented.

The clinical results are indefinite so far as positive beneficial results are concerned.

Stable-gallium toxicity limits the amount of the radioactive gallium that can be administered. Consequently, Ga^{72} is not considered to be an effective therapeutic agent.

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DISSEMINATED LUPUS ERYTHEMATOSUS

Analysis of Thirty-Four Cases

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DISSEMINATED lupus erythematosus is a febrile disease of unknown etiology characterized by dermatological lesions, polyserositis, depression of the bone marrow elements, and widespread visceral involvement. It has a peculiar predilection for young women and usually has a fatal termination. In this report, a relatively large series of cases observed in a short period of time are reviewed in an attempt to present the clinical and laboratory features of the disease.

MATERIAL

Thirty-four cases of disseminated lupus erythematosus have been selected for analysis. In all the clinical course was suggestive of the diagnosis, and every case was proved by pathological examination, by the demonstration of the L. E. cell, or both. Thirty-one cases were observed in the last two years, since L. E. cell technique has been available, and the remaining three were diagnosed and proved at necropsy prior to that time. The 34 cases have been analyzed from the standpoint of clinical and laboratory findings, course of illness, and response to therapy.

HISTORY

More than a century ago, Hebra first described the skin lesions of lupus erythematosus, which he called seborrhea congestiva. Some years later, Casenave applied the name lupus erythematosus to the disease, believing that it represented an erythematous form of cutaneous tuberculosis. In 1872, Kaposi [1] realized the systemic nature of the illness and called attention to the grave prognosis. Before the turn of the century, Osler [2] recorded his brilliant observations and strongly emphasized the visceral manifestations of the disease. In 1924, Libman and Sacks [3] described a nonbacterial verrucous endocarditis in four cases, in two of which there were the typical skin lesions of lupus erythematosus. In 1935, Baehr, Klemperer,

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1. Kaposi, M. K.: Neue Beiträge zur Kenntnis des Lupus erythematosus, Arch. Dermat. u. Syph. **4**:36-78, 1872.

2. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme, Am. J. Med. Sc. **110**:629-646 (Dec.) 1895.

3. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Arch. Int. Med. **33**:701-737 (June) 1924.

and Schifrin [4] reported their findings in 23 cases of lupus erythematosus and correlated the clinical and pathological features of the illness. The following year, Friedberg and associates [5] demonstrated that lupus erythematosus could occur without skin lesions. The criteria for the pathological diagnosis of the disease were then summarized by Klemperer, Pollack, and Baehr in 1941.[6] Although several excellent clinical summaries appeared in the literature,[7] antemortem diagnosis in the absence of a characteristic rash remained speculative. The discovery of the L. E. phenomenon by Hargraves and associates [8] in 1948 facilitated the antemortem diagnosis of the disease. Recently, the introduction of corticotropin (ACTH) and cortisone has provided valuable agents for the treatment of disseminated lupus erythematosus.

CLINICAL FINDINGS

Age and Sex.—The occurrence of the disease in young females of the child-bearing age has been stressed. The predominance of females in other series has varied from 68.7% [7c] to 95.7%.[4] In the present series, 31 of the 34 patients were women, an incidence of 91%. The disease had its onset in 4 of the women before the menarche and in 4 after the menopause; that is, eight of 31 women (26%) were outside the child-bearing age when the disease first developed. This point is stressed because lupus erythematosus is so often referred to as a disease of menstruating women. The age distribution of the present series was as follows:

Below 10, 3	21 to 30, 8	41 to 50, 5
11 to 20, 4	31 to 40, 9	51 to 60, 5

The youngest patient was 3 years of age at the onset (Case 2), and the oldest 56. Whereas other investigators found the greatest incidence in the age group below 30,[9] in the present series, 56% of the patients were above that age limit. The highest incidence occurred in the fourth decade, a finding similar to that of Tumulty and Harvey.[7c]

Predisposing Factors.—Numerous factors have been implicated in the etiology of lupus erythematosus. These include racial background, hypersensitivity, foci of

4. Baehr, G.; Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Assoicated with Lupus Erythematosus and Endocarditis), Tr. A. Am. Physicians **50**:139-155, 1935.

5. Friedberg, C. K.; Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, Arch. Int. Med. **58**:662-684 (Oct.) 1936.

6. Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569-631 (Oct.) 1941.

7. (*a*) Cluxton, H. E., Jr., and Krause, L. A. M.: Acute Lupus Erythematosus Disseminatus, Ann. Int. Med. **19**:843-872 (Dec.) 1943. (*b*) Baehr, G., and Pollack, A. D.: Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **134**:1169-1174 (Aug. 2) 1947. (*c*) Tumulty, P. A., and Harvey, A. M.: The Clinical Course of Disseminated Lupus Erythematosus: An Evaluation of Osler's Contributions, Bull. Johns Hopkins Hosp. **85**:47-73 (July) 1949.

8. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: The Tart Cell and the "LE" Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28 (Jan. 21) 1948.

9. Griffith, G. C., and Vural, I. L.: Acute and Subacute Disseminated Lupus Erythematosus: A Correlation of Clinical and Postmortem Findings in 18 Cases, Circulation **3**:492-500 (April) 1951. Baehr, Klemperer, and Schifrin.[4]

infection, tuberculosis, hormonal imbalance, and photosensitization. Apart from the high incidence of preceding exposure to sunlight or ultraviolet rays, no consistent predisposing factor was evident in this series. All blood cultures were negative for pyogenic bacteria. In two patients who were receiving antibiotics, Aspergillus niger was found. In one of these it was isolated from the lung at necropsy, and in the other it was cultured from the plasma. The presence of this fungus in association with lupus erythematosus has been previously observed,[10] and a relationship between the fungus and antibiotic administration has also been recognized.

Focal infections were encountered in almost half the patients, and active clinical tuberculosis was present in two. Of the nine patients skin-tested for tuberculosis, four showed positive reactions.

A possible hormonal relationship was indicated by the exacerbation of the disease in one patient during pregnancy, with remission following therapeutic abortion (Case 5). However, evidence of hormonal imbalance was absent in all the patients studied.

A familial tendency was suggested by the occurrence of the disease in two members of the same family. In a review of the literature we were able to find only three reports of a familial occurrence of disseminated lupus erythematosus.[11] The role of familial factors is discussed elsewhere.[12]

The patients exhibited an exceedingly diverse racial background, which included seven Jewish, six Italian, four Puerto Rican, three Irish, and two Negro. The remaining patients had family origins in Brazil, Peru, Finland, British Guiana, Hungary, France, Poland, and Holland. With the possible exception of a low Negro incidence, this roughly represents a cross section of the hospital population.

Duration of Illness.—The grave prognosis of disseminated lupus erythematosus has been well recognized. Few patients have survived more than five years. Baehr, Klemperer, and Schifrin [4] reported a maximum duration of four and a half years from onset to death.

In the present analysis, the date of onset was chosen as the time when constitutional symptoms first developed. This was usually in close temporal relationship to the skin lesion, except in those patients in whom a localized discoid lesion antedated the appearance of systemic manifestations by many years. The evolution of a chronic discoid lesion into a disseminated form was recognized by Kaposi, although it has received little mention in the medical literature. Ormsby and Montgomery [13] stated that in 30% of patients with acute and subacute disseminated lupus erythematosus,

10. Haserick, J. R.: Simulation of the Lupus Erythematosus Phenomenon by Materials of Fungal Origins, J. Invest. Dermat. **16**:211-215 (April) 1951.

11. Maschkilleissen, L. N., and Neradow, L. A.: Über Lupus erythematodes familiaris, Dermat Ztschr. **73**:9-13 (Feb.) 1936. Legobbe, E.: Familiärer Erythematodes: (2 Todesfälle, bei einer Beobachtung tuberkulöser Organbefund), Dermat. Wchnschr. **105**:1145-1149 (Sept. 4) 1937. Davis, M. W., and Gutridge, G. H.: Disseminated Lupus Erythematosus in Identical Twin Sisters Associated with Diabetes Mellitus in One Case, J. Missouri M. A. **48**:446-450 (June) 1951.

12. Pirofsky, B., and Shearn, M. A.: The Familial Occurrence of Disseminated Lupus Erythematosus, to be published.

13. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, p. 955.

the disease begins as a chronic discoid lesion. Belote [14] expressed the belief that the chronic discoid and the acute disseminated forms merely represent variations of the same disease. However, Baehr [15] stated that "in spite of its name this disease bears no relationship whatsoever to . . . discoid lupus." In the present series, six patients previously exhibited facial skin eruptions diagnosed as chronic discoid lupus erythematosus. For periods up to 25 years the lesions remained localized and the patient had no systemic complaints. When symptoms of disseminated lupus erythematosus first occurred, the skin lesion usually began to spread to other parts of the face and body and to mucous membranes. Preceding exposure to sunlight could be implicated as the precipitating cause for the dissemination in only one instance.

A brief report of a relevant case is presented.

CASE 1.—A 36-year-old white woman entered University Hospital with complaints of arthralgia, dyspnea, cough, and peripheral edema. At the age of 23, after exposure to sunlight, a cutaneous eruption developed over the bridge of the nose and the malar prominences of the face. This lesion was diagnosed as chronic discoid lupus erythematosus. Although the lesion persisted, the patient remained in perfect health for 13 years. Two weeks before admission she noted pain and stiffness of the small and medium-sized joints of the body, with diarrhea, fatigue, and dyspnea. Examination revealed an erythematous eruption with slight scar formation over the butterfly area of the face and the extensor surfaces of the arms. There were rales at both lung bases, an enlarged liver, superficial adenopathy, and tenderness with slight swelling of the wrists and the interphalangeal joints of both hands.

Laboratory examination showed hemoglobin 10 gm., red cells 3,100,000, and white cells 4,900, with a normal differential count; erythrocyte sedimentation rate 99 and 112 (Westergren); albumin-globulin ratio 3.5/4.3, and no L. E. cells.

The patient was treated with cortisone, 100 mg. a day, and showed a good response, but symptoms returned when the dose was decreased. The patient was discharged on maintenance doses of cortisone. Since that time, L. E. cells have been demonstrated in the peripheral blood.

Of the 34 patients in this series, 14 have died, and in these the average duration of illness was 6 years and 4 months, with a range of 7 weeks to 20 years (Case 2). Each of two patients lived 10 years, and another survived for 15 years.

Symptomatology.—In view of the pathological alteration in the connective tissue throughout the body, it might be expected that signs and symptoms of disseminated lupus erythematosus would be polymorphic. The patients in the present series manifested extremely varied findings. These are summarized in Tables 1 and 2.

The rash of disseminated lupus erythematosus usually consists of bright-red, superficial, coalescent patches which show little tendency to atrophy or scar formation. It may involve almost any part of the body or mucous membranes but at some stage is usually present over the butterfly area of the face and the V-area of the neck. Associated alopecia is fairly common. Cutaneous lesions were present in 31 (91%) of the patients in this study. Eighteen of these gave a history of preceding exposure to sunlight or ultraviolet rays. The lesions were confined to the face in only 11, whereas spread to other parts of the body was noted in 20. The lesions were present in the mouth in 13 patients, with actual ulceration noted in 10. Characteristic erythematous lesions about the fingernails, nail beds, and thenar and hypothenar eminences were seen in nine patients. Alopecia occurred in 13. Purpura,

14. Belote, G. H.: Lupus Erythematosus Disseminatus: Its Present Status, Arch. Dermat. & Syph. **39**:793-806 (May) 1939.

15. Baehr, G.: Disseminated Lupus Erythematosus, in Cecil, R. L., and Loeb, R. F.: A Textbook of Medicine, Ed. 8, Philadelphia, W. B. Saunders Company, 1951, p. 483.

TABLE 1.—*Frequency of Symptoms in Thirty-Four Patients with Disseminated Lupus Erythematosus*

Symptoms	No. with Symptoms	%
Weakness	33	97
Anorexia	29	85
Arthralgia	29	85
Dyspnea	27	80
Cough	25	74
Weight loss	25	74
Chest pain	22	65
Sunlight sensitivity	18 *	58
Arthritis	18	53
Pleuritic pain	17	50
Nausea and vomiting	17	50
Menstrual disorders	13 †	48
Orthopnea	15	44
Abdominal pain	12	35
Diarrhea	9	27
Epistaxis	8	24
Hemoptysis	6	18
Photophobia	6	18

* Observations on 31 patients.
† Observations on 27 patients.

TABLE 2.—*Frequency of Signs in Thirty-Four Patients with Disseminated Lupus Erythematosus*

Signs	No. with Signs	%	
Fever: Septic	24	71	100
Fever: Low-grade	10	29	100
Skin lesions	31	91	
Systolic murmur	24	71	
Lymphadenopathy	23	68	
Pedal edema	18	53	
Mental changes	17	50	
Rales	16	47	
Optic abnormalities	16	47	
Chronic infections	16	47	
Hepatomegaly	15	44	
Splenomegaly	14	41	
Enlarged heart	14	41	
Hypertension	11	32	
Funduscopic abnormalities	9 *	28	
Hypotension	9	27	
Pleural effusion	8	24	
Congestive failure	8	24	
Gallop rhythm	7	21	
Pericardial rub or effusion	6	18	
Purpura	5	15	
Convulsions	5	15	
Ascites	5	15	
Apical diastolic murmur	4	12	
Jaundice	4	12	
Precordial thrill	4	12	
Arthritic deformities	4	12	
Nephrotic syndrome	4	12	
Parotitis	3	9	
Raynaud's syndrome	2	6	

* Observations on 32 patients.

a not uncommon finding in lupus erythematosus, was present in five patients; in four it was associated with thrombocytopenia (e. g. Case 6).

Constitutional symptoms such as anorexia, fever, weakness, and weight loss were extremely common. Although completely afebrile periods were encountered, fever at some time was present in all the patients. Ten patients had a low-grade fever, but in the majority the temperature was septic in character and late afternoon spikes to 104 F. or over were frequent. The hyperthermia was often associated with bronchopneumonia and pleurisy, and toxic psychoses were not uncommon.

Polyserositis is an integral part of the disease and is reflected in the frequent occurrence of arthralgia, pleuritis, pericarditis, and ascites. The arthritis may attack one or many joints. Migratory polyarthritis is common and may be indistinguishable from rheumatic fever. Although the pain usually occurs without objective joint findings, more than half the patients in this series had varying degrees of heat, swelling, and, occasionally, redness. The joints usually did not respond to salicylates and occasionally resisted corticotropin (ACTH) and cortisone, a point which should help to distinguish the condition from rheumatic polyarthritis. Rarely joints may suffer actual deformities.[16] In four of the patients in the present series deformities developed which were similar to the changes observed in rheumatoid arthritis (e. g. Case 4).

Findings suggestive of pulmonary pathology were extremely prominent. Cough and chest pain were frequent complaints. The chest pain was usually sharp and pleuritic. Occasionally it was substernal and similar to coronary pain. Frank hemoptysis was encountered in six patients, pulmonary tuberculosis being implicated in only one.

The importance of abdominal symptoms was stressed by Osler[2] in his classic paper on the erythema group. In this series, nausea, vomiting, and diarrhea were common. Abdominal pain was noted in 12 cases and at times led to the diagnosis of acute surgical abdomen. Because signs of peritoneal irritation were often absent, and because the underlying disease process was known, unnecessary surgery was avoided. Perihepatitis, perisplenitis, and abdominal adenopathy have been implicated in initiating the abdominal pain. The superficial lymph nodes were found to be significantly enlarged in 23 cases. Hepatomegaly was noted in 15 cases and splenomegaly in 14. Jaundice was present in four cases. In one viral hepatitis was suspected, and in another necropsy revealed an associated miliary tuberculosis with hepatic involvement. No cause was found in the remaining two.

Mental changes were observed in one-half the patients, the majority having severe depression. This occurred even in the absence of fever. Generalized convulsions were seen in five patients. Their cause was not known, but in two of the patients severe hypertension was implicated (e. g. Case 3).

Attention has been focused on the heart in this disease since the work of Libman and Sacks.[3] About 30% of patients with disseminated lupus erythematosus are found at postmortem examination to have the atypical verrucous endocarditis which those writers described. As yet there is no method by which Libman-Sacks endocarditis may be diagnosed in the living patient.

Systolic murmurs are common in disseminated lupus erythematosus, but in the presence of fever and anemia they are difficult to evaluate. Of the 34 patients in

16. Friedberg, Gross, and Wallach.[5] Cluxton and Krause.[7a]

this series, systolic murmurs were present in 24. Although occasionally harsh, the murmurs were more often soft and blowing in quality and were usually loudest at the apex.

In four of the patients, auscultation revealed a diastolic murmur at the cardiac apex. It occurred in one during presystole and in the remaining three during early or middiastole. Necropsy was performed on two of these patients, and in both Libman-Sacks endocarditis of the mitral valve was found. In the case with the presystolic rumble, four small vegetations were present on the auricular surface of the mitral valve near the free margin. The chordae tendineae and the free margins of the mitral valve were thickened. In the second case in which a blowing middiastolic murmur was described, the auricular surface of the aortic leaflet of the mitral valve was slightly thickened and small verrucae were present near the free margin. No evidence of rheumatic heart disease was found in either case.

Libman and Sacks [8] described a loud presystolic rumble in Case 4 of their series and the postmortem examination revealed thickening of the mitral valve with vegetations; Aschoff bodies were absent. In a case cited by Tumulty and Harvey,[7c] a sound was heard in diastole which was interpreted as a diastolic murmur, and at necropsy the mitral valve was found to be considerably altered by verrucous vegetations. The fact, however, that diastolic murmurs in lupus erythematosus may not be due to Libman-Sacks endocarditis is illustrated by a case described by Griffith and Vural [9] in which a late apical diastolic murmur was found at necropsy to have been due to rheumatic mitral stenosis.

Symptoms and signs of congestive failure were fairly frequent, and the heart was demonstrably enlarged in 14 patients. Gallop rhythm was detected in seven patients and a pericardial rub in six. Hypertension was encountered in 11. In five of these, the elevated blood pressure was associated with severe renal disease. In one patient, hypertension was related to toxemia of pregnancy, and in another it developed during cortisone therapy and persisted after discontinuation of this therapy. No cause was found in the remaining four patients, although two of them were over 40 years of age and may have had associated essential hypertension. Arrhythmias were rarely found. In one patient (Case 3) auricular flutter developed during pericarditis, and in another patient auricular fibrillation developed late in the course of her disease. Premature contractions were never detected either clinically or by electrocardiogram.

The alterations in the electrocardiogram that have been described in disseminated lupus erythematosus are prolongation of the P-R and Q-T intervals, low voltage, left axis deviation, and T wave abnormalities.[17] In the present series, one or more electrocardiograms were available in 29 cases. In no case was the P-R interval prolonged. Flattening or inversion of the T waves was the most commonly encountered abnormality. The findings are summarized in Table 3.

Funduscopic abnormalities have been noted in disseminated lupus erythematosus.[18] Maumenee [19] described three typical lesions: (1) small, fluffy, yellowish-

17. Liebow, I. M., and Feil, H.: The Electrocardiogram in Lupus Erythematosis Disseminatus, Am. J. Med. **3**:44-49 (July) 1947.

18. Wagener, H. P.: Retinal Lesions in Acute Disseminate Lupus Erythematosus, Am. J. M. Sc. **211**:240-244 (Feb.) 1946.

19. Maumenee, A. E.: Retinal Lesions in Lupus Erythematosus, Am. J. Ophth. **23**:971-981 (Sept.) 1940.

white to white spots located in the superficial layers of the retina, shown histologically to be cytoid bodies; (2) small hemorrhages situated superficially in the retina, and (3) slight papilledema. Of the 32 patients on whom funduscopic examination was done, hemorrhages and exudates were found in 9 and papilledema in 1. Other optic abnormalities were frequently seen. Photophobia was complained of by five patients and pain and excessive tearing by a similar number. Conjunctivitis was noted in five and subconjunctival hemorrhages in two.

The general debilitation of the patients was believed to explain the high incidence of chronic infections such as skin abscesses, indolent ulcers, and otitis media. The same factor may be implicated in the occurrence of lobar or bronchial pneumonia, which frequently complicated the clinical course. Since the advent of corticotropin (ACTH) and cortisone in the treatment of disseminated lupus erythematosus, this tendency toward infection assumes great importance.

TABLE 3.—*Electrocardiographic Findings on Twenty-Nine Patients with Disseminated Lupus Erythematosus*

Findings		No. with Findings		%
Abnormal tracing		21		72
T wave abnormalities		20		69
Deviation of electrical axis:	left	13	45	52
	right	2	7	
Sinus tachycardia		14		48
Prolonged Q-T (corrected)		6		21
Elevated S-T segments		3		10
Low voltage		3		10
Auricular fibrillation		1		3
Auricular flutter		1		3
Prolonged P-R		0		0
Prolonged QRS		0		0

Chronic, nonsuppurative parotitis was present in three patients. It was bilateral in two and unilateral in the third. The parotid glands were enlarged, firm, tender, and painful in each case. A thorough investigation uncovered no apparent cause for this disorder. We are unaware of any reports in the literature of a similar occurrence. In one patient the parotitis had been present for five years and represented the chief complaint on admission to the hospital (Case 3).

Of the 27 women of menstruating age, 13 complained of menstrual disturbances, mainly amenorrhea. This symptom was most prominent during the acute febrile stage, and normal menses usually recurred with remission.

The renal lesions in disseminated lupus erythematosus represent an extremely important aspect of the disease.[20] Montgomery and McCreight [21] found "renal irritation, nephrosis, or nephritis" in 100% of their acute cases and in 69% of their subacute cases.

20. Stickney, J. M., and Keith, N. M.: Renal Involvement in Disseminated Lupus Erythematosus, Arch. Int. Med. **66**:643-660 (Sept.) 1940. Daugherty, G. W., and Baggenstoss, A. H.: Syndrome Characterized by Glomerulonephritis and Arthritis: Libman-Sacks Disease with Predominantly Renal Involvement, Arch. Int. Med. **85**:900-923 (June) 1950.

21. Montgomery, H., and McCreight, W. G.: Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. **60**:356-372 (Sept.) 1949.

Four of the patients in the present series had a clinical variant of the nephrotic syndrome. Each had anasarca, hypoalbuminemia, and heavy proteinuria, but hypercholesterolemia was not prominent. Three patients had cholesterol levels within the normal range, and in the fourth an initial value of 420 mg. per 100 ml. later decreased to 250 mg. The latter patient has been reported on in detail by Brenner, Leff, and Hochstein.[22]

Another interesting feature of this nephrotic state was the association of hypertension in all and azotemia in each of the three patients on whom blood nonprotein nitrogen determinations were performed. This situation is not unlike that which may occur in diabetic glomerulosclerosis and in renal amyloidosis.

Three of the four patients with the nephrotic syndrome have died, and autopsies have been performed on two. Lesions of chronic glomerulonephritis were demonstrated in both.

TABLE 4.—*Laboratory Findings in Disseminated Lupus Erythematosus*

Laboratory Finding or Test	No. of Patients	No. with Abnormality	%
Elevated sedimentation rate	34	34	100
Biopsy of skin lesion	13	13	100
Anemia	34	33	97
L. E. cell	31	29	94
Coombs test	4	3	75
Prothrombin time	8	6	75
Leucopenia	34	25	74
A/G ratio	29	20	69
Proteinuria	34	21	62
Eosinopenia	34	18	53
Tuberculin test	9	4	44
Rumpel-Leede test	7	3	43
Hematuria	34	12	35
Thrombocytopenia	16	5	31
Wassermann test	26	5	19
Elevated NPN	29	5	17
Clotting time	7	0	0
Bleeding time	7	0	0
Cryoglobulinemia	3	0	0

Laboratory Findings.—The laboratory findings noted in this series (Table 4) did not differ appreciably from those reported by others.

The sedimentation rate was accelerated in each patient studied. The values were usually markedly increased and with rare exceptions remained elevated even during clinical remissions. A significant degree of anemia was found in each patient but one. It was most often normochromic and normocytic. Hemoglobin levels below 9 gm. were obtained in 11 patients. In three of these, a hemolytic anemia had been suspected, and the Coombs test was positive in all three (e. g. Case 5). During cortisone therapy the Coombs test became negative in one of these patients. Depression of the leucocytes below 5,000 was noted in 25 patients at some time during their course. The white cell count rose during intercurrent infection and at times exceeded 20,000. This rise was usually due to an absolute increase in neutrophiles. The underlying leucopenia was thereby masked and did not become evident

22. Brenner, J. J.; Leff, W. A., and Hochstein, E.: Lupus Erythematosus Disseminatus Sine Lupo with the Nephrotic Syndrome, Am. J. Med. **5**:288-297 (Aug.) 1948.

until the concurrent illness was controlled. Eighteen of the patients had eosinopenia. In one patient with 15% eosinophiles, there was an associated parasitic infestation. The platelet count was determined for 16 patients, and in 5 there was thrombocytopenia with a count below 150,000. Prothrombin time determinations, done for eight, showed abnormal prolongation for six. The Rumpel-Leede test was performed on seven patients and on three was positive. No abnormalities in bleeding or clotting time were observed in the patients tested.

Skin biopsies performed for 13 patients with cutaneous lesions revealed changes compatible with disseminated lupus erythematosus in all. Biopsy reports on two patients without skin lesions revealed normal skin.

Proteinuria was found to be present in 21 of the 34 patients (62%). In addition, five patients had trace amounts of protein in their urine. Hematuria was found in 12 instances. In 10 it was microscopic, and in 2 it was gross. Pyuria and cast formation were frequently observed. Fixation of the specific gravity was an infrequent finding.

Of 29 patients whose blood nonprotein nitrogen was determined, 5 showed abnormal elevations. Coburn and Moore [23] demonstrated alterations of the plasma proteins in all cases they studied. In the present series, 20 of 29 patients had abnormal albumin-globulin ratios.

Positive serological reactions for syphilis were encountered in 43% of cases in a reported series.[23] In the present series, the reactions of three patients were reported as positive and of two as doubtful; however, one of the positive reactors was believed to have latent syphilis.

THE L. E. CELL

The L. E. cell was first demonstrated in 1948 in the bone marrow of patients with disseminated lupus erythematosus [8] and was subsequently found in the peripheral blood.[24] In acute disseminated lupus erythematosus the L. E. cell is almost invariably demonstrated; only eight cases have been reported in which L. E. cell preparations were negative.[25] The L. E. cell has been found to decrease and occasionally disappear during clinical remissions. Soffer and associates [26] reported that the L. E. cell disappeared in only 1 of 14 patients treated with corticotropin (ACTH) or cortisone, whereas Haserick [27] found that it disappeared in 5 of 16 similarly treated patients.

There are few reports of positive L. E. cell preparations in diseases other than disseminated lupus erythematosus.[28] Montgomery and McCreight [21] stated that the

23. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196-221 (Sept.) 1943.

24. Sundberg, R. D., and Lick, N. B.: "L. E." Cells in the Blood in Acute Disseminated Lupus Erythematosus, J. Invest. Dermat. **12**:83-84 (Feb.) 1949.

25. Smith, P. A. J.: The "L. E. Cell" and Its Significance, Brit. J. Dermat. **64**:10-25 (Jan.) 1952.

26. Soffer, L. J.; Levitt, M. F., and Baehr, G.: Use of Cortisone and Adrenocorticotropic Hormone in Acute Disseminated Lupus Erythematosus, Arch. Int. Med. **86**:558-573 (Oct.) 1950.

27. Haserick, J. R., in Mote, J. R., editor: Proceedings of the Second Clinical ACTH Conference, Philadelphia, Blakiston Company, 1951, Vol. 2, p. 685.

28. Beerman, H.: The L. E. Cell and Phenomenon in Lupus Erythematosus, Am. J. Med. Sc. **222**:473-481 (Oct.) 1951.

L. E. phenomenon was found in a case of myelomatosis, but this diagnosis has since been doubted.[25] Berman and co-workers[29] found L. E. cells in one case each of pernicious anemia, dermatitis herpetiformis, and chronic discoid lupus. However, they indicated that the cells were not more numerous than 1 to 500 neutrophiles. This is in contrast to the high concentration of L. E. cells found in the acute stage of systemic lupus. Kurnick is said to have found the L. E. cell in a case of miliary tuberculosis.[30] Lee and associates[30] found it in a case of hemolytic anemia of unknown etiology. The spleen, removed operatively, failed to show histological evidence of lupus erythematosus, and on this basis they considered the test as false-positive. On the other hand, Haserick[10] and Barnes and co-workers[31] could find no instance of a false-positive test in several hundred patients tested. Smith,[25] after reviewing the literature, concluded that demonstration of the L. E. cell may be regarded as a specific test for systemic lupus erythematosus.

In the present series, L. E. cells were searched for by means of a standard technique[32] in 31 cases. In 29 of these cases the cell was demonstrated, an incidence of 94%. The diagnosis of disseminated lupus erythematosus in the remaining two cases rests on the following criteria: The first patient, a 36-year-old white woman, had all the clinical criteria for the diagnosis of subacute disseminated lupus erythematosus. Numerous L. E. cell preparations were negative. Necropsy later demonstrated the typical changes of disseminated lupus erythematosus. The other patient, clinically suspected of having subacute disseminated lupus erythematosus, had a nephrectomy for a complicating hypernephroma. The unaffected kidney tissue revealed typical wire-loop changes.

All of the patients observed while in the acute stage of the disease had positive tests for L. E. cells. In five the L. E. cell was not found initially but occurred only after exacerbation of the disease. With clinical improvement, L. E. cells decreased in number, and on three occasions they disappeared entirely from the blood. A rough parallelism was noted between the acuteness of the disease and the quantity of L. E. cells present. This finding is in accord with the observation that L. E. cells are frequently not found in the subacute phase of the illness.[31]

The findings in the present series supported the general opinion that the L. E. cell technique is a sensitive and highly specific test for the presence of acute disseminated lupus erythematosus.

THERAPY

Until recently, the treatment of disseminated lupus erythematosus was mainly supportive. With the introduction of corticotropin (ACTH) and cortisone, many

29. Berman, L.; Axelrod, A. R.; Goodman, H. L., and McClaughry, R. I.: So-Called "Lupus Erythematosus Inclusion Phenomenon" of Bone Marrow and Blood: Morphologic and Serologic Studies, Am. J. Clin. Path. **20**:403-418 (May) 1950.

30. Lee, S. L.; Michael, S. R., and Vural, I. L.: The (L. E.) Lupus Erythematosus Cell: Clinical and Chemical Studies, Am. J. Med. **10**:446-451 (April) 1951.

31. Barnes, S. S.; Moffatt, T. W.; Lane, C. W., and Weiss, R. S.: Studies on the L. E. Phenomenon, Arch. Dermat. & Syph. **62**:771-785 (Dec.) 1950.

32. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus, J. Invest. Dermat. **11**:209-213 (Sept.) 1948. Mathis, H. B.: A Simple Office Procedure for Demonstrating Lupus Erythematosus Cells in Peripheral Blood, Blood **6**:470-473 (May) 1951.

reports of favorable response appeared in the literature.[33] Patients have shown a prompt decrease in fever and subsidence of joint symptoms, cutaneous lesions, and serous effusions. There are usually an associated feeling of well-being, improvement in the appetite, and a gain in weight. Many patients can be carried into a clinical remission and then maintained by daily hormonal therapy. Despite these obvious improvements, laboratory abnormalities usually persist.

Of the 34 patients in this series, 20 were treated with corticotropin or cortisone. Ten received corticotropin, seven cortisone, and three both. The results were encouraging in 14 and fair to poor in the remainder. All but two patients showed an initial response characterized by defervescence and decrease in toxemia. The skin lesions subsided in all but three of the treated patients. Although joint symptoms promptly improved in all, arthralgia later developed in two patients and arthritis in one during adequate maintenance dosage. Four of the group died while receiving the drug. Two additional patients with marked renal impairment, who responded initially, became refractory to therapy and died shortly after it was discontinued. Attention has been directed to the disappointing results with corticotropin and cortisone in cases of disseminated lupus erythematosus with renal insufficiency.[34]

Severe toxic effects of the hormone were encountered infrequently. In two patients fluid retention developed and precipitated congestive failure, and in a third patient hypertension developed during therapy and persisted for a known period of two months.

In all but one patient proteinuria persisted during therapy. Leucopenia and anemia were occasionally reversed. L. E. cells disappeared in four patients but returned in one. After remission during corticotropin therapy, one patient whose blood had consistently shown L. E. cells had negative L. E. preparations on weekly testing for five months.

In addition to the hormones, antibiotics were extensively employed. These have a real value in a disease in which poor healing and infections are so frequently encountered.

Blood transfusions were administered to 17 patients, with an unusually high incidence (36%) of transfusion reactions. Reactions to transfused blood in disseminated lupus erythematosus have previously been observed.[35]

REPORT OF CASES

The bizarre signs and symptoms of disseminated lupus erythematosus often lead to erroneous diagnoses. In this series, the correct diagnosis was usually made in the presence of a characteristic rash, but in its absence a variety of incorrect diagnoses

33. Johnson, S. A. M., and Meyer, O. O.: The Treatment of Lupus Erythematosus Disseminatus with Cortisone, Am. J. Med. Sc. **223**:9-15 (Jan.) 1952. Dubois, E. L.; Commons, R. R.; Starr, P.; Stein, C. S., and Morrison, R.: Corticotropin and Cortisone Treatment for Systemic Lupus Erythematosus, J. A. M. A. **149**:995-1002 (July 12) 1952. Soffer, L. J., and Bader, R.: Corticotropin and Cortisone in Acute Disseminated Lupus Erythematosus: Results of Long-Term Use, J. A. M. A. **149**:1002-1008 (July 12) 1952. Soffer, Levitt, and Baehr.[26] Haserick.[27]

34. Thorn, G. W.; Merrill, J. P.; Smith, S.; Roche, M., and Frawley, T. F.: Clinical Studies with ACTH and Cortisone in Renal Disease, Arch. Int. Med. **86**:319-354 (Sept.) 1950.

35. Callender, S.; Race, R. R., and Paykoc, Z. V.: Hypersensitivity to Transfused Blood, Brit. M. J. **2**:83-84 (July 21) 1945.

were tendered. In this connection, the skin lesion was not evident in 14 cases (41%) when systemic symptoms became manifest. Three of these cases were representative of the *sine lupo* type in that cutaneous lesions never developed. The initial incorrect diagnoses were: in five cases rheumatic fever, in three, rheumatoid arthritis, and in the remainder chronic glomerulonephritis, subacute bacterial endocarditis, thrombocytopenic purpura, sarcoidosis, fever of unknown origin, and blood dyscrasia of unknown type.

In most cases several organ systems are affected; however, predominant localization in one system is not unusual. Thus, one may see lupus erythematosus with almost all the signs and symptoms directed toward the kidney, the joints, or the heart.

Several case histories are presented in summary form to illustrate certain features of the disease.

CASE 2.—A 23-year-old white woman was admitted to Bellevue Hospital because of polyarthritis. At the age of 3 pain and swelling of her joints had occurred and was diagnosed as rheumatic fever. During childhood and adolescence she experienced exertional dyspnea and had many febrile episodes accompanied by arthralgia and arthritis. Rheumatic heart disease was diagnosed. Eight months before death she entered Bellevue Hospital for the first time, complaining of polyarthritis. Anemia, leucopenia, proteinuria, and acceleration of the sedimentation rate were found. Therapeutic doses of salicylates were administered, but the joint swelling failed to subside. In addition, her course was complicated by the development of pneumonia and pleural effusion. While she was in the hospital, a transient erythema appeared over the butterfly area of the face. She was discharged improved and was well until another episode of acute migratory polyarthritis developed and she reentered the hospital. Examination revealed no evidence of the previous rash. The patient was acutely toxic, with a temperature of 104 F. and blood pressure of 95/50. Dullness and crackling rales were present at both lung bases. The heart was enlarged, and there was a regular sinus tachycardia. A Grade 2 apical systolic murmur was found. There was no peripheral edema. Cervical adenopathy was present, but no hepatosplenomegaly.

Laboratory examinations revealed: hemoglobin 10 gm.; red cells 3,830,000; white cells 2,150; differential count normal; erythrocyte sedimentation rate (Westergren) 102, and 3+ protein and rare blood cells in the urine. An electrocardiogram revealed left axis deviation.

The patient ran a febrile course, unresponsive to penicillin and massive doses of acetylsalicylic acid. She went rapidly downhill, and died on the 21st hospital day.

Necropsy showed disseminated lupus erythematosus with atypical endocarditis of the mitral valve, acute and chronic pericarditis, chronic bilateral pleuritis, generalized necrotizing arteritis, and periarterial fibrosis of the spleen. There was no pathological evidence of rheumatic fever.

This young woman was believed to have acute rheumatic fever and rheumatic heart disease. She had an unusually long history of repeated episodes of polyarthritis from the age of 3 to her death at 23. The diagnosis of rheumatic heart disease was made on every examination until the rash appeared five months before death. The correct diagnosis might have been suspected before the appearance of the rash because of anemia, leucopenia, severe proteinuria, and failure of salicylates to cause remission of joint symptoms.

CASE 3.—A 26-year-old white woman was admitted to Bellevue Hospital because of parotitis, fever, cough, and chest pain. She had been well until five years previously, at which time bilateral, painful, parotid swelling occurred and persisted. This was variously diagnosed as mumps, sarcoid, and glandular fever. One month before admission, the parotid swelling increased and became quite painful. In addition, migratory polyarthritis, chest pain, and fever

developed. The patient was referred into the hospital with a tentative diagnosis of sarcoid. Examination revealed an acutely ill young woman. The temperature was 102 F., the blood pressure 140/70, and the pulse 100 and regular. There was an erythematous eruption across the bridge of the nose and the malar areas. Both parotid glands were firm, tender, and swollen, and a moderate degree of trismus was present. Stensen's duct was clear, and no pus could be expressed upon compression of the parotid gland. The fundi were normal. The area of cardiac dullness was increased. The heart sounds were fair, and there was a moderately loud, blowing systolic murmur, heard best at the pulmonic area. The liver and spleen were not palpable, and no adenopathy was present.

Laboratory examination showed: hemoglobin 9 gm.; red cells 3,170,000; white cells 4,300; differential count normal; erythrocyte sedimentation rate (Westergren) 109; albumin-globulin ratio 2.5/5.1; specific gravity of the urine 1.010; a trace of protein and occasional red blood cells in the urine; nonprotein nitrogen 30 mg. per 100 ml.; Wassermann reaction negative, and abundant L. E. cells in the peripheral blood. X-ray examination of the parotids for calculus and culture of material from the parotid duct were negative. X-rays of the bones revealed no abnormalities.

The hospital course was stormy, characterized by chest and joint pains and severe toxemia. Pericardial and pleural effusions developed. Administration of cortisone was started, with a prompt decrease in temperature and joint symptoms. On the ninth day of cortisone therapy cardiac tamponade developed. The nonprotein nitrogen had risen to 90 mg. per 100 ml., and the urine now contained numerous red blood cells. Cortisone therapy was discontinued, and two pericardial taps removed 1,000 cc. of serosanguineous fluid. The patient was discharged against advice but returned one week later, complaining of severe dyspnea and palpitations. The temperature was 102 F., and the blood pressure was 160/96. The rash was absent, and parotid swelling was now limited to the right side. The fundi showed hemorrhages, exudates, and papilledema. The pericardial and pleural effusions were still present. Hepatomegaly and ascites were now noted. The specific gravity of the urine had become fixed at 1.010, and there were 1+ proteinuria and many red blood cells; the nonprotein nitrogen was 69 mg. per 100 ml. An electrocardiogram now showed auricular flutter with varying degrees of block. L. E. cells were still present in the peripheral blood. The blood pressure progressively rose, and convulsions ensued. On the 40th hospital day the patient was again discharged against advice.

One week later she entered another hospital and died shortly afterward. Necropsy [36] revealed bilateral pleural adhesions, pulmonary edema, interstitial pneumonitis, adhesive fibrinous pericarditis, myocardial hypertrophy, dilation of the right side of the heart, ascites, and chronic glomerulonephritis. Unfortunately, the parotid glands were not examined.

This patient's illness was characterized by toxemia, fever, polyarthritis, pericardial and pleural effusions, and a typical rash of disseminated lupus erythematosus. In addition, she had anemia, leucopenia, hematuria, proteinuria, elevation of the sedimentation rate, inversion of the albumin-globulin ratio, and many positive L. E. cell preparations. Despite the classic picture of systemic lupus erythematosus, pathological findings were nonspecific. The case illustrates the fact that specific pathological lesions may be absent in disseminated lupus erythematosus.[37]

Another interesting feature in this case was the severe parotitis of five years' duration for which no cause was found. Before the rash developed, this finding led to a diagnosis of Boeck's sarcoid. Despite the many similarities between the two diseases, the toxic clinical course and the severe renal involvement in the presence

36. Dr. Antonio Rottino, St. Vincent's Hospital, New York, performed the necropsy.

37. Klemperer, P., in discussion on Ginzler, A., and Fox, T. T.: Disseminated Lupus Erythematosis in a Youth with Some Unusual Findings, Arch. Path. **26**:918 (Oct.) 1938. Ginzler, A. M., and Fox, T. T.: Disseminated Lupus Erythematosus: Cutaneous Manifestation of Systemic Disease (Libman-Sacks); Report of Case, Arch. Int. Med. **65**:26-50 (Jan.) 1940. Cluxton and Krause.[7a]

of polyserositis favors the diagnosis of lupus erythematosus. In addition, the parotitis of Boeck's sarcoid is painless. Lack of histopathological examination of the parotid gland prevents any definite conclusion as to the nature of the changes in this rare complication.

CASE 4.—A 33-year-old white woman entered Bellevue Hospital complaining of cough, hemoptysis, chest pain, and fever. She had been well until two years before admission, when arthralgia of the hands and elbows and exertional dyspnea developed and she lost 20 pounds (9 kg.). She entered another hospital, where a persistent fever was recorded. An extensive work-up was unrevealing, and the patient was discharged with a diagnosis of fever of unknown origin and rheumatoid arthritis. During the ensuing two years Raynaud's syndrome and deformity of the fingers developed. Examination revealed a pale thin woman with a blood pressure of 90/70 and a temperature of 102 F. No skin rash was noted. The skin of the fingers was white, tense, and cold, and flexion deformities were present. The left elbow showed limitation of motion with ankylosis at 140 degrees. Breath sounds were absent in the lower third of both lungs. A Grade 2 blowing systolic murmur was audible throughout the precordium. Moderate adenopathy was present, and the liver and spleen were palpable.

A blood count showed hemoglobin 8 gm., red cells 2,500,000, and white cells 4,000, with neutrophiles 81%, lymphocytes 8%, and monocytes 11%. The erythrocyte sedimentation rate (Westergren) was 48 and the albumin-globulin ratio 3.8/4.3. Urinalysis disclosed a specific gravity of 1.018, a trace of protein, and no red blood cells. The Wassermann reaction was positive. A tuberculin test was negative. Both the sheep cell and the hemolytic streptococcus agglutination test were negative. A chest x-ray revealed obliteration of the left costophrenic angle and enlargement of the heart. X-rays of the wrists, hands, hypopharynx, esophagus, stomach, and duodenum were normal. An electrocardiogram revealed inverted T waves in leads II, aV_F, and V_1 through V_4. Biopsy of the skin over the fingers revealed normal tissue. L. E. cells were demonstrated in the peripheral blood.

The hospital course was characterized by low-grade fever with occasional afternoon elevations in temperature. The patient was treated symptomatically and discharged unimproved after one month. Two months later the patient died at home; no necropsy was performed.

Because disseminated lupus erythematosus so frequently affects the joints and may produce actual deformity, rheumatoid arthritis is often diagnosed erroneously. Although a cutaneous lesion never developed in this patient, the diagnosis was suggested by the following clinical findings: fever, arthritis, pleural effusion, adenopathy, hepatomegaly, splenomegaly, elevation of the sedimentation rate, marked anemia, leucopenia, reversal of the albumin-globulin ratio, and a false-positive Wassermann reaction. The demonstration of numerous L. E. cells in the blood provided confirmation of the diagnosis. The tense white skin over the fingers superficially resembled scleroderma; however, complete investigation for this condition gave negative results. The skin changes were believed to be secondary to the chronic Raynaud's phenomenon.

CASE 5.—A 25-year-old white woman was well until five months before admission, when a rash over the butterfly area of the face developed and spread after ultraviolet ray treatment. The patient then consulted her physician, who administered cortisone, after which the rash cleared on the face but appeared over the chest, back, arms, and legs. Two months later the patient entered Bellevue Hospital for the first time, because of fever, weakness, and amenorrhea. She had a mild anemia, leucopenia, and elevation of the sedimentation rate. The urine contained 2+ protein. L. E. cells were not found in her blood at this time. A 10-week pregnancy was discovered and a therapeutic abortion performed. After this procedure, the skin lesions resolved completely and the systemic symptoms subsided dramatically.

Three months later she was readmitted to Bellevue Hospital with a two-week history of anorexia, weakness, nausea, and vomiting. The blood pressure was 120/68 and the temperature

101 F. Examination revealed pigmented skin lesions over the face, back, arms, and finger tips. There was generalized lymphadenopathy, and the spleen was palpable 9 cm. below the left costal margin.

Examination of the blood disclosed hemoglobin 5 gm., red cells 1,400,000, white cells 1,800, transitional cells 5%, neutrophiles 15%, lymphocytes 69%, monocytes 4%, eosinophiles 7%, and reticulocytes 8.4%. The erythrocyte sedimentation rate (Westergren) was 144 and the albumin-globulin ratio 3.3/7.3. Urinalysis showed a specific gravity of 1.023, a trace of protein, a trace of sugar, and occasional red blood cells. Blood platelets numbered 380,000. The bleeding time was three-fourths minute (Duke), clotting time five minutes (capillary tube), Rumpel-Leede test negative, prothrombin time 14 seconds, icterus index 12, and Coombs test strongly positive. L. E. cells were now found in the peripheral blood.

The patient ran a febrile course, with the temperature averaging 101.5 F. Six transfusions of whole blood were administered in the first two weeks, with negligible effect upon the blood count. Corticotropin (ACTH) therapy, 25 mg. every six hours, was started. On the fourth day of therapy the temperature spiked to 105 F. and she complained of severe pain in the abdomen and chest. On the sixth day of corticotropin she became extremely toxic, confused, and dyspneic. X-rays revealed bronchopneumonia of the left lower lobe and a left pleural effusion. Corticotropin therapy was discontinued, and antibiotics and oxygen were administered along with 1 liter of whole blood. She gradually improved, gained weight, and three weeks later became afebrile for the first time. Although she was greatly improved symptomatically, the anemia persisted, with the hemoglobin level at 7 gm.; the Coombs test remained positive, and L. E. cells were still present in the peripheral blood. The patient was discharged to the clinic.

This case illustrates disseminated lupus erythematosus with the predominant systemic findings limited to the hematologic system. In the absence of the skin lesion, the cause for the acquired hemolytic anemia might well have remained unknown. This clinical picture of lupus erythematosus has been reported as a presenting complaint.[38] Recently, Conley[39] summarized the blood disorders in association with disseminated lupus erythematosus.

Corticotropin and cortisone were seemingly without benefit in this case, and the remission occurred spontaneously. This case also suggests a hormonal relationship in the disease, as evidenced by the clinical improvement following termination of pregnancy.

Case 6.—A 17-year-old Puerto Rican girl had been in good health until nine months before admission, when severe epistaxis, gingival bleeding, and purpura developed. She also complained of fever and joint pains. She entered another hospital, where examinations revealed a platelet count of 70,000, bleeding time of 7 minutes, clotting time of 11 minutes, no clot retraction, positive Rumpel-Leede test, and negative sickling and red cell fragility tests. The fever and arthralgia aroused suspicion, and L. E. cells were searched for and found in the sternal marrow. Administration of corticotropin (ACTH) was started, and the bleeding tendency subsided as the platelet count rose to 200,000. The fever and joint symptoms subsided but recurred after discontinuation of corticotropin therapy. These symptoms were then partially controlled by acetylsalicylic acid, and she was transferred to Bellevue Hospital. Examination revealed a thin, pale girl with a temperature of 102.4 F. and blood pressure of 130/40. No rash or purpura was present. Generalized lymphadenopathy was the only abnormal finding.

Laboratory examinations showed: hemoglobin 10.2 gm.; red cells 3,600,000; white cells 9,400 (decreased to 3,500 on the fourth day); a normal differential count; erythrocyte sedimentation rate (Westergren) 36; albumin-globulin ratio 2.7/4.8; 1+ protein and rare red blood cells in the urine; bleeding and clotting time normal; platelets adequate; clot retraction normal;

38. Dubois, E. L.: Acquired Hemolytic Anemia as the Presenting Syndrome of Lupus Erythematosus Disseminatus, Am. J. Med. **12**:197-204 (Feb.) 1952.

39. Conley, C. L.: Disorders of the Blood in Disseminated Lupus Erythematosus, Am. J. Med. **12**:1-2 (July) 1952.

prothrombin time prolonged; a 4+ Wassermann reaction, and L. E. cells still present in the peripheral blood.

The hospital course was characterized by high fever and severe joint pains. A bedsore developed which showed a poor tendency to heal. On the 15th hospital day an erythematous eruption appeared over the bridge of the nose, malar areas, and fingers. Corticotropin was administered and brought relief of the arthralgia and recession of the skin rash. When the daily dose was lowered, pain in the abdomen and chest developed and the arthralgia returned. After 15 weeks of hospitalization the patient was discharged, with L. E. cells still abundant in the peripheral blood.

Despite a presenting picture that resembled a primary blood dyscrasia, the diagnosis of disseminated lupus erythematosus was made almost immediately. This fact illustrates the importance of an awareness of the varied patterns in which the disease may appear. Thrombocytopenic purpura is a well-recognized guise of disseminated lupus erythematosus and was present in 12% of this series. The value of the L. E. test is demonstrated in this case, for it supplied strong corroborative evidence of the diagnosis nine months before the characteristic lupus rash made its appearance.

The return of symptoms following the withdrawal or lowering of corticotropin dosage emphasizes the necessity for adequate drug levels when long-term maintenance therapy is required.

SUMMARY

Thirty-four cases of disseminated lupus erythematosus are analyzed from the standpoint of clinical and laboratory features and response to therapy. In each the diagnosis was established by suggestive clinical and laboratory findings. In addition, every case was confirmed by demonstration of the L. E. cell, pathological material, or both.

The age of onset varied from 3 to 56 years; 19 of the patients were over 30. Of the 31 women, 8 (26%) were outside the child-bearing age.

Predisposing factors are reviewed. Preceding exposure to sunlight or ultraviolet rays was implicated in 18 of the 31 patients with skin lesions. Two patients had clinical tuberculosis, and two had A. niger infections. In one patient a remission followed therapeutic abortion. The racial background of the patients was exceedingly diverse.

Among the patients who died, the average duration of illness was found to be six years and four months. A range of 7 weeks to 20 years was encountered.

The symptomatology was varied and often bizarre. All patients had fever, and 31 had skin lesions. A nephrotic state was present in four patients. Chronic, nonsuppurative parotitis was noted in three patients. Six patients had a history of a preceding skin eruption which was believed to be chronic discoid lupus erythematosus.

Cardiac symptoms were found to be prominent. Congestive failure occurred in 8 and hypertension in 11. Systolic murmurs were common. Two patients with diastolic apical murmurs were found at necropsy to have had Libman-Sacks endocarditis. The electrocardiogram was considered abnormal for 21 of 29 patients.

The sedimentation rate was elevated in all patients and all but one had anemia. Other abnormal laboratory findings included leucopenia in 74%, an abnormal

albumin-globulin ratio in 69%, proteinuria in 62%, hematuria in 35%, and a positive Wassermann reaction in 19%. Three patients clinically suspected of hemolytic anemia had a positive Coombs test.

L. E. cells were found in 29 of the 31 patients who were tested, an incidence of 94%. When the patients were acutely ill, L. E. cells were regularly demonstrable. With improvement or remission, the cells usually decreased in number and occasionally disappeared from the blood and marrow.

Twenty of the patients received corticotropin (ACTH) or cortisone. The results were encouraging in the majority. However, four patients died while receiving the hormones; two patients who responded initially later became refractory to the treatment and died.

Case histories are presented in order to illustrate some of the features of disseminated lupus erythematosus. Because systemic manifestations so frequently precede the rash (in 41%), the importance of a high index of suspicion is stressed.

Dr. Marion B. Sulzberger, chairman, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and director of service, University Hospital, and Dr. E. Hugh Luckey, director, Second Medical (Cornell) Division, Bellevue Hospital, gave permission for a report of cases in their services.

Miss Hazel Mathis and Miss Florence Simm assisted in the preparation of the L. E. slides.

Progress in Internal Medicine

ANTIBIOTIC THERAPY IN INFECTIONS OF THE RESPIRATORY TRACT

Use of Penicillin, Including Aerosol, Dust, and Diethylaminoethyl Iodide Penicillin; and Aureomycin, Terramycin, and Chloramphenicol in Bronchiectasis, Bronchitis, Sinusitis, Bronchial Asthma and Pulmonary Emphysema

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I. Penicillin

THE INTENTION of this paper is to appraise the value of antibiotic treatment in chronic bronchial infections. Patients with bronchial asthma and pulmonary emphysema frequently suffer from associated chronic bronchitis. In other cases of chronic bronchitis bronchospasm of slight to moderate extent is often present. Similarly, patients with bronchiectasis at times manifest bronchospasm and variable degrees of pulmonary emphysema. The results of treatment of these clinical entities with penicillin, especially by inhalation, and with aureomycin, terramycin, and chloramphenicol (chloromycetin®) will be presented, as well as a preliminary statement of the use of the diethylaminoethyl ester of penicillin.

The use of antibiotic drugs in bronchiectasis has been restricted in some clinics to the treatment of febrile episodes and the preparation of these patients for surgery.[1] Although the management of chronic infection in bronchopulmonary disease poses complex problems, the use of the antibiotic agents and procedures which are now available results in some cases in dramatic clinical improvement, including recovery from a semi-invalid state and relief of severe dyspnea. Despite the fact

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This article has been shortened for publication in the ARCHIVES by the omission of Table 3. This will appear in the authors' reprints.

From the Department of Medicine, Presbyterian Hospital, Columbia University College of Physicians and Surgeons, and the Columbia Division, Goldwater Memorial Hospital.

The diethylaminoethyl ester of penicillin was furnished by the Smith, Kline & French Laboratories.

The soluble tablets of crystalline penicillin, which have been found convenient for aerosol administration by patients at home, were supplied to us by the Commercial Solvents Corporation and the Premo Pharmaceutical Laboratories, Inc.

The antibiotic drugs aureomycin, terramycin, and chloramphenicol (chloromycetin®) were supplied by the Lederle Laboratories Division, American Cyanamid Company; Charles Pfizer & Company, Inc., and Parke, Davis & Company. Penicillin was provided by E. R. Squibb & Sons and by Sharp & Dohme, Inc. The funds employed in the investigation were contributed by Cornelius Crane Jr., and by the Josiah Macy Jr. Foundation.

1. Harter, J. S.: Treatment of Lung Abscess, J. Internat. Coll. Surgeons **13**:1910, 1950. Stewart, J. D., and Kennedy, P. A.: Problem of Bilateral Multilobar Bronchiectasis, New York J. Med. **50**:1829, 1950. Muschenheim, C., in Textbook of Medicine, Ed. 7, edited by R. L. Cecil, W. McDermott, and H. G. Wolff, Philadelphia, W. B. Saunders Company, 1947, p. 926.

that hazards are admittedly present in an indiscriminate employment of various antibiotics, it must be emphasized that the favorable effects achieved in many patients with appropriately regulated therapy cannot be obtained by such routine measures as postural drainage, use of expectorant and bronchodilator drugs, or change of climate.

Although operative removal of the affected lobes of the lung in bronchiectasis results in dramatic cure of the disease, the majority of cases are not suitable for surgery; in the series reported by Badger,[2] 59% of 400 cases were not considered acceptable for operation. Bradshaw and associates [3] reported that the mortality prior to adequate antibiotic therapy was 34.5% of 171 patients observed between 1925 and 1935; these careful studies were based on clinical material in which bronchoscopic drainage and excellent general medical care were provided, except that antibiotic therapy was then not available. In the cases reported by Perry and King [4] the nonsurgically treated patients had a mortality over a 12-year period of 26%, 41% of deaths having occurred within 5 years of the time of hospitalization.

The medical aim of treatment for patients with bronchiectasis who are not suitable for operation is the attempt to maintain the patient as free from infection as is clinically feasible. Some of the patients with multilobar bronchiectasis who were placed under aerosol therapy in our clinic in 1944 have continued to manifest a striking clinical gain in health and well-being. Similarly, the control of bronchial infection in pulmonary emphysema and bronchial asthma has been found to be of crucial importance in obtaining not only a remission in the symptoms of the disease but, in some cases, a long-lasting increase in respiratory function, manifested by lessened dyspnea on exertion and a decrease in the incidence and severity of bronchospasm. The scope and limitation of antibiotic aerosol therapy, which has been modified somewhat since our earlier studies were reported,[5] will first be presented.

PHYSICAL AND PHYSIOLOGICAL BASIS OF AEROSOL THERAPY

The purpose of inhalation of nebulized solutions is to deposit small droplets of therapeutic substances suspended in air or oxygen on the respiratory passageway and the alveoli. Heubner,[6] who made careful observations in 1920 on the effect of particle size on the site of deposition of inhaled nebulized substances, concluded that particles of relatively small size are deposited in the smallest bronchi, whereas those of larger size are lodged in the upper respiratory passageway. He nebulized a

2. Badger, T. L.: Bronchiectasis, New England J. Med. **237**:937, 1947.

3. Bradshaw, H. H.; Putney, F. J., and Clerf, L. H.: Fate of Patients with Untreated Bronchiectasis, J. A. M. A. **116**:2561, 1941.

4. Perry, K. M., and King, D. S.: Bronchiectasis: A Study of Prognosis on the Follow-up of 400 Patients, Am. Rev. Tuberc. **41**:531, 1940.

5. (*a*) Barach, A. L.; Silberstein, F.; Oppenheimer, E. T.; Hunter, T., and Soroka, M.: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**:485, 1945. (*b*) Garthwaite, B., and Barach, A. L.: Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis, Am. J. Med. **3**:261, 1947. (*c*) Barach, A. L., and Garthwaite, B.: Physiologic and Antibiotic (Penicillin) Therapy in Chronic Hypertrophic Pulmonary Emphysema, Dis. Chest **13**:91, 1947.

6. Heubner, W.: Über Inhalation zerstaubter Flussigkeiten, Ztschr. ges. exper. Med. **10**:269, 1919.

solution of malachite green into a cat and found the green color in some alveoli. Castex, Capdehourat, and Pedace [7] nebulized into the lungs of rabbits a solution of brilliant cresyl blue, which they then recovered in the phagocytes. Krueger and associates [8] nebulized solutions of radioactive chromic phosphates into monkeys and, after freezing sections of the lung, made x-ray photographs which showed that the inhaled nebulized substances were uniformly distributed throughout the lungs.

Lageder,[9] in 1933, observed a rise in vital capacity in patients with asthma, with clinical improvement, after inhalation of a nebulized 1:1,000 epinephrine hydrochloride solution. The introduction by Graeser and Rowe [10] in 1935 of a glass hand-bulb nebulizer and the employment of 1:100 epinephrine hydrochloride solution made this method of treatment a practical and relatively effective therapeutic procedure for patients with mild or moderate bronchospasm. Administration of larger doses of 1% phenylephrine (neo-synephrine®) hydrochloride and 1 to 2% epinephrine to patients with severer asthma was shown to produce a substantial increase in the vital capacity, as well as in the velocity of air movement, especially during the expiratory cycle.[11] A more visually stable mist of epinephrine was produced by the addition of 10 to 50% glycerin,[12] but whether lowering the vapor pressure of droplets by the addition of glycerin is, in fact, clinically more effective in patients with asthma has not been conclusively proved.

Studies on the effectiveness of drugs administered as aerosols progressed especially in South America,[13] and, more recently, in Europe.[14] Harris and co-workers [15] sprayed microcrystals of sulfathiazole into the lungs with an atomizer and demonstrated that significantly high blood levels ensued. The sulfonamide aerosols were

7. Castex, M. R.; Capdehourat, E. L., and Pedace, E. A.: Inhalación de substancias nebulizados: Comprobación experimental de su poder de penetración a nivel del aparato respiratorio, Arch. argent. enferm. ap. respir. y tuberc. **9**:1, 1941.

8. Krueger, A., and Lyons, W. R.: Inhalatory Route for Prophylaxis and Treatment of Experimental Influenza: Distribution of Inhaled Material; Immune Serum in Prophylaxis and Treatment, Am. J. M. Sc. **207**:40, 1944.

9. Lageder, K.: Untersuchungen über den Einfluss inhalierten Adrenalins auf die Lungenventilation beim Asthma bronchiale und über dessen Allgemeinwirkung, Beitr. Klin. Tuberk. **83**:605, 1933.

10. Graeser, J. B., and Rowe, A. L.: Inhalation of Epinephrine for Relief of Asthmatic Symptoms, J. Allergy **6**:415, 1935.

11. Barach, A. L.: Physiological Methods in Diagnosis and Treatment of Bronchial Asthma and Pulmonary Emphysema, Ann. Int. Med. **12**:454, 1938. Richards, D. W., Jr.; Barach, A. L., and Cromwell, H. A.: Use of Vaporized Broncho-Dilator Solutions in Asthma and Emphysema: A Continuous Inhalation Method for Severe Asthmatic States, Am. J. M. Sc. **199**:225, 1940.

12. Abramson, H. A.: Improved Inhalational Therapy of Asthma, Arch. Phys. Therapy **21**:612, 1940.

13. Castex, M. R.; Capdehourat, E. L., and Laverello, A.: Nuevo tratamiento de las supuraciones broncopulmonares: Acción curativa de un preparado sulfamídico nebulizado, Rev. asoc. méd. argent **55**:85, 1941.

14. Dautrebande, L.: Aerosols medicamenteux, Paris, Masson & Cie, 1946. Lock, A.: Aerosols in Theory and Practice, Prantosol Products, Ltd., London, 1944. Biancani, E., and Delaville, G.: Les aerosols, l'Expansion scientifique francaise, Paris, 1946. Rooth, G.: Inhalation of Liquid Aerosols, Acta med. scandinav., Supp. 228, 1949.

15. Harris, T. N.; Sommer, H. E., and Chapple, C. C.: Administration of Sulfonamide Micro-Crystals by Inhalation, Am. J. M. Sc. **205**:1, 1943. Chapple, C. C., and Lynch, M. M.: A Study of Sulfonamide Aerosol Inhalation, ibid. **207**:488, 1944.

used clinically by Barach and colleagues,[16] who showed that the inhalation of nebulized solutions of glucosulfone sodium (promin®) prevented the development of experimental tuberculosis in guinea pigs. Glucosulfone sodium solutions were used as aerosols in patients with pulmonary and laryngeal tuberculosis by Edlin and associates.[17] Stacey [18] and Applebaum [19] recorded significant improvement after inhalation of nebulized sulfathiazole solutions in patients with bronchiectasis.

Drinker and co-workers,[20] Gardner,[21] and others studied industrial hazards due to dust and investigated the deposition of finely divided particles in the respiratory tract of man and animals. According to calculations of Findeisen,[22] 65% of particles 0.3 μ in radius are exhaled and those of 1 to 3 μ in radius are for the most part absorbed in the lungs. Using silica dust, which admittedly has a density 2.5 times that of water, Van Wijk and Patterson [23] found that this solid particulate material, with a radius of 0.5 μ, was retained in the lungs to the extent of 63% after inhalation, that particles between 0.6 and 2 μ in radius were retained to the extent of 63 to 96%, and that particles 0.3 μ in radius were retained in the respiratory tract to the extent of approximately 30%.

Measurements of the site and degree of the retention of radioactive nebulized solutions were first made in man by Talbot, Quimby, and Barach.[24] Radioactive sodium, which emits penetrating gamma rays, was quantitated by means of the Geiger-Mueller counter placed over the axilla. The counts were made immediately after inhalation of the aerosol, the maximum concentration being present at this time, rapidly decreasing during the first half-hour and diminishing more slowly for the ensuing three hours. The count in the axilla immediately after inhalation of the aerosol was three times as high as that found after equilibrium had been obtained between the chest and the rest of the body.

Studies by Barach, Garthwaite, and Bickerman [25] showed that blood concentrations of inhaled sulfathiazole aerosols varied with the mass mean radius of the droplets. When aerosols with a mass mean radius of 1.3 to above 3.1 μ were

16. Barach, A. L.; Molomut, N., and Soroka, M.: Inhalation of Nebulized Promine in Experimental Tuberculosis, Am. Rev. Tuberc. **46**:268, 1942. Barach, A. L.: Physiologic Therapy in Respiratory Disease, Ed. 2, Philadelphia, J. B. Lippincott Company, 1948.

17. Edlin, S. J.; Bobrowitz, I. D.; Safford, F. D., Jr., and Butler, F. S.: Promin Inhalational Therapy in Pulmonary Tuberculosis, Am. Rev. Tuberc. **1**:543, 1944.

18. Stacey, J. W.: Inhalation of Nebulized Solutions of Sulfonamides in Treatment of Bronchiectasis, Dis. Chest **9**:302, 1943.

19. Applebaum, I. L.: Treatment of Bronchial Lesions by Inhalation of Nebulized Solutions of Sodium Sulfathiazole, Dis. Chest **10**:415, 1944.

20. Drinker, P.: Size-Frequency and Identification of Certain Phagocytosed Dusts, J. Indust. Hyg. & Toxicol. **7**:305, 1925. Drinker, P.; Thomson, R. M., and Fitchett, J. M.: Determination of Suspensoids by Alternating-Current Precipitators, ibid. **7**:261, 1925.

21. Gardner, L. U.: Reaction to Inert Dusts, Saranac Laboratory Symposium on Silicosis, 1939, p. 143.

22. Findeisen, W.: Über das Absetzen kleiner, in der Luft suspendierter Teilchen in der menschlichen Lunge bei der Atmung, Arch. ges. Physiol. **236**:367, 1935.

23. Van Wijk, A. M., and Patterson, H. S.: Percentage of Particles of Different Sizes Removed from Dust-Laden Air by Breathing, J. Indust. Hyg. & Toxicol. **22**:31, 1940.

24. Talbot, T. R., Jr.; Quimby, E. H., and Barach, A. L.: Method of Determining the Site of Retention of Aerosols Within the Respiratory Tract of Man by Use of Radioactive Sodium, Am. J. M. Sc. **214**:585, 1947.

25. Barach, A. L.; Garthwaite, B., and Bickerman, H.: Studies on Aerosol Deposition, Postgrad. Med. **5**:341, 1948.

employed, the blood concentration was progressively higher as the particle size diminished. The sputum concentrations were higher when the nebulizers were used that produced medium-sized aerosol particles, i. e., vaponefrin,* mass mean radius 2.5 μ, and DeVilbiss, mass mean radius 3.1 μ, as compared with the small-particle size (SPS) nebulizer, mass mean radius 1.3 μ.[26]

In a study of homogeneous aerosols of glycerin and water with sodium chloride, nuclei containing a trace of radioactive sodium were produced with an aerosol of particle size varying from 0.2 to 2.6 μ in radius. Deposition in the alveoli and small bronchi was found to be related to particle size, since the axillary counts were four times as high, in the range of 0.4 to 0.8 μ in radius, the maximum count being found with a particle size of 0.8 μ in radius.[27] In an experiment in which the subject inhaled an aerosol containing 50,000 units of crystalline sodium penicillin in 1 cc. of isotonic sodium chloride solution containing a trace of radiosodium, the axillary radiations were in good agreement with those obtained in a control experiment without penicillin.

A method of introducing antibiotic aerosols into nasal accessory sinuses was developed by producing an intermittent negative pressure of 60 mm. Hg in the antra (maxillary sinuses).[28] When subjects with oral-antral fistulas were used, the penicillin recovered from the antrum after exposure to 50,000 units of penicillin aerosol varied from a trace to 7,000 units, which represented only a small portion of the penicillin introduced into the antrum, since the larger part clings to the mucous membrane and is absorbed. This method of introducing penicillin aerosol into the sinuses has been found of value by others in the treatment of both acute and chronic sinusitis.[29]

Factors which govern the distribution and retention of aerosols in the respiratory tract, other than the particle size of the mist, include the breathing pattern of the subject; the density, surface tension, and hygroscopic property of the solution; the vapor pressure and the temperature of the aerosol; the location of areas of turbulence in the respiratory passageway; the nature of the drug itself; the pressure at which the nebulizer is operated, and the density of the gas which is employed to

26. The determination of the mass mean radius of particles for the nebulizers employed was carried out by Dr. I. B. Wilson.

27. Wilson, I. B., and LaMer, V. K.: Retention of Aerosol Particles in the Human Respiratory Tract as a Function of Particle Radius, J. Indust. Hyg. & Toxicol. **30**:265, 1948.

28. Barach, A. L.; Garthwaite, B.; Soroka, M., and Anderson, F. F.: Apparatus for Introduction of Penicillin Aerosol into the Nasal Accessory Sinuses, Ann. Int. Med. **24**:97, 1946. Barach, A. L.; Garthwaite, B.; Rule, C.; Talbot, T. R., Jr.; Kernan, J. D.; Babcock, J., and Brown, G.: Penicillin Aerosol and Negative Pressure in Treatment of Sinusitis, Am. J. Med. **1**:268, 1946. Barach, A. L.; Rumsey, C. C., Jr.; Soroka, M., and Rader, D: A Simplified Technique of Treatment of Sinusitis with Penicillin Aerosol, with a Description of a Foot Pump for Economical Nebulization of Penicillin and Other Therapeutic Aerosols, New York J. Med. **47**:1498, 1947; **46**:1703, 1946.

29. McAuliffe, G. W., and Mueller, G. C.: Aerosol Penicillin Administered in Paranasal Sinusitis with Balanced Suction and Pressure, Arch. Otolaryng. **46**:67, 1947. Davis, D.: Inhalation of Penicillin and Streptomycin in Office Practice, Tr. Am. Acad. Ophth. **52**:273, 1948. Pons, E. R., Jr.; Glass, W. M., and Garthwaite, B.: An Evaluation of Aerosol-Negative Pressure Therapy Given Once Daily in Chronic Purulent Sinusitis, J. A. M. A. **139**:766, 1948. Hynes, F. J.: Penicillin Aerosol Therapy in Sinusitis, Ann. Otol. Rhin. & Laryng. **58**:189, 1949.

generate the aerosol.[30] Thus, a particle formed from a hygroscopic solution may take on water and increase in size as it enters the warm saturated area within the respiratory tract. On the contrary, particles from a nonhygroscopic solution may become smaller through evaporation.

The breathing pattern of the subject has been shown to modify the absorption of penicillin; thus, inhalation of a chemotherapeutic aerosol through the mouth alone results in higher absorption in the lungs than when the nose and mouth are employed [25]; areas of turbulence in the nasal passages result in deposition of the drug in substantial amounts in the nasal passageway and also in the nasopharynx. Although Mutch [30a] reported a case in which the sulfonamide excretion was higher after inhalation of the aerosol through the nose than through the mouth, our results on blood levels of sulfonamides and penicillin indicate that the oral route of inhalation results in greater deposition of those drugs both in the bronchial mucous membrane and in the alveoli.[25] Deep breathing produces substantially higher blood levels of penicillin than does normal breathing. In five subjects who inhaled 50,000 units of penicillin, the average serum concentration one-half hour later was 0.08 unit per cubic centimeter during deep breathing and 0.04 unit per cubic centimeter during normal breathing.

PRINCIPLES OF ADMINISTRATION OF THERAPEUTIC AEROSOLS

The selection of the aerosol with optimal particle size for therapeutic administration depends not only on the location where deposition is desired but also on the therapeutic substance employed. In the treatment of bronchospasm it is desirable to use a nebulin of bronchodilator solution of relatively small particle size (preferably 1 to 3 μ in radius) in order to obtain both local application to the smaller bronchi and absorption from the alveoli into the blood stream; in addition, it is desirable to avoid the use of a vasoconstricting nebulin of large particle size in order to prevent useless, and at times irritating, deposition of drug on the pharynx, larynx, and trachea.

In the treatment of bronchopulmonary infections with penicillin aerosol, application of the drug to the surface of the bronchial mucous membrane, as well as absorption from the alveoli into the blood stream, should be provided; this also appears to be best accomplished by inhalation of mists of relatively small particle size, 1 to 3 μ in radius. Although maximum alveolar absorption as measured by blood concentration takes place with an aerosol of even smaller particle size, 0.8 μ radius,[27] the sputum concentration of the drug employed appears to be slightly lower with aerosols with a mass mean radius of 1.3 μ.[25] Of more importance clinically is the fact that the longer time required for administration of very small particles

30. (*a*) Mutch, N.: Inhalation of Chemotherapeutic Substances, Lancet **2**:775, 1944. (*b*) Wilson, I. B.: Deposition of Charged Particles in Tubes, with Reference to the Retention of Therapeutic Aerosols in the Human Lung, J. Colloid. Sc. **2**:271, 1947. (*c*) Abramson, H. A.: Principles and Practice of Aerosol Therapy of the Lungs and Bronchi, Ann. Allergy **4**:440, 1946. (*d*) Abramson, H. A., and Demerec, M.: Method for Experimental Control of Particle Size of Therapeutic Aerosols, J. Allergy **16**:184, 1945. (*e*) Knott, F., and Clark, W.: Absorption of Aerosol Penicillin via the Lungs, Lancet **1**:468, 1945. (*f*) Gaensler, E. A.; Beakey, J. F., and Segal, M.: Pharmacodynamics of Pulmonary Absorption in Man: Aerosol and Intratracheal Penicillin, Ann. Int. Med. **31**:582, 1949.

(mass mean radius 1.0 μ) is tiring for the patient, with the small-particle-size nebulizer now available. Since bronchial infection is best combated, in our opinion, by an effective antibiotic blood level in the capillaries supplying the diseased area, as well as by a high local concentration on the mucous membrane and in the bronchial secretions, nebulizers that provide droplets of moderate size (2 to 3 μ) seem preferable. However, when treatment of nasopharyngeal and sinus infections is intended, an antibiotic aerosol of larger particle size is desirable in order to obtain greater deposition of the drug in the nasopharynx and, with use of intermittent negative pressure, in the sinus cavities themselves.

The use of sulfonamide aerosols has been largely superseded by that of aerosols of antibiotic drugs, especially penicillin, because of its greater clinical effectiveness and lower toxicity. That penicillin aerosol was absorbed in the lungs and excreted in the urine in a normal subject and in rabbits was demonstrated by Bryson and associates.[31] In the original report on penicillin aerosol from our clinic,[5a] the following observations on principles and methods of administration were made: 1. Penicillin-aerosol administration in concentrations of 50,000 units per cubic centimeter did not produce discernible harmful effects on the lungs of rats. 2. Rats were protected against intraperitoneal injection of lethal doses of a hemolytic Streptococcus by a single inhalation of 25,000 units. 3. Administration of penicillin aerosol to 20 patients and miscellaneous controls revealed no convincing evidence of an irritant effect on the lungs, although soreness of the tongue and increased coughing (in asthmatic subjects) were encountered. 4. By the passing of oxygen through a Y-tube, penicillin nebulized during the inspiratory cycles resulted in demonstrable blood levels after inhalation of 50,000 units in 1 cc. of saline solution. 5. Inhalation of penicillin in adequate dosage was found to be clinically effective in the majority of cases of bronchopulmonary infection, especially bronchiectasis, bronchitis, and lung abscess, and in some cases of bronchial infection occurring in bronchial asthma and pulmonary emphysema. 6. It was demonstrated that Gram-positive organisms were consistently absent from the sputum culture after four to six days of treatment and that subsequently Gram-negative organisms, such as Escherichia coli and Pseudomonas aeruginosa (Bacillus pyocyaneus), were recovered from sputum cultures. The pathogenic significance of the secondary appearance of these Gram-negative organisms did not appear to be of great moment at that time, since patients generally manifested clinical improvement notwithstanding their presence. However, Abraham and Chain [32] and Woodruff and Foster [33] demonstrated that these bacteria elaborated an enzyme, penicillinase, which interfered with the bacteriostatic activity of penicillin when present in sufficiently high concentration. Infections with Gram-negative bacteria have, at times, occurred during penicillin treatment [34]; this will be discussed later. In general, the reports on

31. Bryson, V.; Sansome, E., and Laskin, S.: Aerosolization of Penicillin Solutions, Science **100**:33, 1944.

32. Abraham, E. P., and Chain, E.: Enzyme from Bacteria Able to Destroy Penicillin, Nature, London **146**:837, 1940.

33. Woodruff, H., and Foster, J. W.: Microbiological Aspects of Penicillin: VII. Bacterial Penicillinase, J. Bact. **49**:7, 1945.

34. Weinstein, L.: Spontaneous Occurrence of New Bacterial Infections During the Course of Treatment with Streptomycin or Penicillin, Am. J. M. Sc. **214**:56, 1947.

penicillin aerosol confirmed the value of the inhalation of penicillin in the treatment of infections in the respiratory tract.[35]

CLINICAL RESULTS OF PENICILLIN THERAPY

Bronchiectasis and Chronic Bronchitis.—The special value of penicillin aerosol in cases of bronchiectasis, particularly inoperable, advanced, or moderately advanced bilateral forms, depends upon (1) the high sputum levels of penicillin after aerosol administration, in contrast to the absence of penicillin in the expectoration after intramuscular injections of the drug; (2) the facility of long-continued administration of penicillin by the patient when taken as an aerosol; (3) its effectiveness in overcoming the development of resistant strains of Micrococcus pyogenes var. aureus (Staphylococcus aureus); (4) the antibiotic effect of local application to the infected bronchial mucous membrane when the capillary blood supply to the bron-

35. (*a*) Olsen, A. M.: Nebulized Penicillin: Preliminary Report of Its Role in the Management of Surgical Bronchiectasis, Proc. Staff Meet., Mayo Clin. **20**:184, 1945, with discussion by O. T. Clagett; (*b*) Streptomycin in the Treatment of Chronic Bronchiectasis: Preliminary Report, ibid. **21**:53, 1946. (*c*) Segal, M. S., and Ryder, C. M.: Penicillin Aerosolization in the Treatment of Serious Respiratory Infections, New England J. Med. **233**:747, 1945. (*d*) Segal, M. S.; Levinson, L., and Miller, D.: Penicillin Inhalation Therapy in Respiratory Infections, J. A. M. A. **134**:762, 1947. (*e*) Vermilye, H. N.: Aerosol Penicillin, ibid. **129**:250, 1945. (*f*) Southwell, N.: Inhaled Penicillin in Bronchial Infections, Lancet **2**:225, 1946. (*g*) Bobrowitz, I. D.; Edlin, J. S.; Bassin, S., and Woolley, J. S.: Penicillin in the Treatment of Bronchiectasis: A Preliminary Report, New England J. Med. **234**:141, 1946. (*h*) Levine, E. R.: Inhalation Therapy in Chronic Bronchial Infections, Dis. Chest **13**:295, 1947. (*i*) Prigal, S. J.: Studies with Medicated Aerosols, Ann. Int. Med. **28**:814, 1948. (*j*) Hagens, E. W.; Karp, M., and Farmer, C. J.: Inhalation Method of Penicillin Therapy: Preliminary Report, Arch. Otolaryng. **41**:333, 1945. (*k*) Finke, W.: Simplification of Penicillin Aerosol Therapy for Home Treatment, Am. Pract. **1**:643, 1947. (*l*) Anderson, D. H., and di Sant'Agnese, P. E. A.: Celiac Syndrome: IV. Chemotherapy of the Respiratory Infection Associated with Cystic Fibrosis of the Pancreas; Penicillin and Drugs of the Sulfonamide Group with Special Reference to Penicillin Aerosol, Am. J. Dis. Child. **72**:17, 1946. (*m*) Barach, A. L.: Physiologic and Antibiotic Therapy of Bronchial Asthma, Connecticut M. J. **11**:819, 1947. (*n*) Allan, W. B.: Bronchiectasis: Modern Treatment, South. M. J. **41**:1049, 1948. (*o*) Bryson, V., and Grace, E. J.: Aerosol Therapy of Respiratory Disease: A Report of 50 Cases, New England J. Med. **237**:683, 1947. (*p*) Knott, F. A., and Southwell, N.: Aerosol Penicillin in the Oxygen Tent, Arch. Dis. Childhood **21**:16, 1946. (*q*) Prigal, S. J.: A Combined Steam Generator and Aerosolizer: The Production of Aerosols of Penicillin, Sulfadiazine, Aminophyllin and Other Medications in Solution, J. A. M. A. **121**:398, 1946. (*r*) Miller, M. W.: Penicillin in Intractable Asthma, J. Allergy **18**:109, 1947. (*s*) Fullerton, C. W., and Shane, S. J.: Treatment of Acute and Chronic Pulmonary Disease with Penicillin Aerosol, Canad. M. A. J. **54**:535, 1946. (*t*) Barach, A. L.; Garthwaite, B., and Rule, C.: Use of Penicillin Aerosol in Bronchopulmonary and Sinus Infections, New York J. Med. **46**:1703, 1946. (*u*) Gaensler, E. A.; Beakey, J. F., and Segal, M. S.: Relative Effectiveness of Parenteral Intratracheal and Aerosol Penicillin in Chronic Suppurative Disease of the Lung, J. Thoracic Surg. **18**:546, 1949. (*v*) Segal, M. S.: Management of the Patient with Severe Bronchial Asthma, Springfield, Ill., Charles C Thomas, Publisher, 1950. (*w*) Veach, O. L.: Aerosol Treatment with Penicillin and Streptomycin, Rocky Mountain M. J. **44**:816, 1947. (*x*) Bickerman, H. A.; Stone, J., and Schilaro, A. J.: Aerosol Penicillin in the Treatment of Chronic Lung Abscess, Am. J. Med. **8**:2, 1950. (*y*) Farber, J. E., and Ross, J.: Use of Aerosol Penicillin and Streptomycin in Bronchopulmonary Infections, California Med. **73**:214, 1950. (*z*) Cardon, L.; Lemberg, L., and Greenebaum, R. S.: Acute Suppurative Bronchitis and Bronchiolitis in Chronic Pulmonary Disease: Diagnosis and Management, Ann. Int. Med. **34**:3, 1951. (*a'*) Eastlake, C., Jr.: Aerosol Therapy in Sinusitis, Bronchiectasis and Lung Abscess, Bull. New York Acad. Med. **26**:423, 1950.

chial wall is impaired by fibrosis, in which case intramuscular injection of the drug may fail to arrest the surface growth of bacteria.

The clinical results of inhalation of penicillin aerosol are summarized in Table 1 from previous studies in our clinic on patients with bronchiectasis, chronic bronchitis, lung abscess and sinusitis.[36] Of 70 cases of bronchiectasis, marked or moderate improvement took place in 58. Of 50 cases of chronic bronchitis without bronchospasm, significant improvement was obtained in 46. However, in 200 cases of chronic bronchitis in association with bronchial asthma or pulmonary emphysema, marked or moderate benefit was observed in 87. The persistence of bronchospasm interfered with complete relief of the symptoms of cough and expectoration in cases in which allergic, as well as infectious, factors played an etiological role.

The indications for treatment in cases of chronic productive cough, with or without bronchospasm, include the demonstration of pus cells in the sputum or nasal secretions, as well as the presence of Gram-positive organisms on culture. The elimination of inflammatory swelling of the bronchial mucous membrane, when due to an infectious process, presumably constitutes the chief mechanism by which dyspnea is relieved in chronic bronchopulmonary disease. Decrease in the incidence

TABLE 1.—*Clinical Results with Penicillin Aerosol in Bronchopulmonary and Sinus Disease*

	No. of Cases	Improvement Due to Penicillin Aerosol		
		Marked	Moderate	Slight or None
Bronchiectasis	70	33	25	12
Lung abscess	11	6	0	5
Chronic bronchitis	50	27	19	4
Chronic bronchitis with bronchial asthma or pulmonary emphysema	200	47	50	103
Acute sinusitis	40	27	9	4
Chronic sinusitis	150	56	57	37

of bronchospasm, however, is a critical factor in some cases of so-called infectious asthma. Antibiotic therapy is apt to be of less value when the nasal discharge and the bronchial expectoration are predominantly of allergic origin, unless infection is definitely indicated by the presence also of numerous polymorphonuclear (not eosinophilic) leucocytes on smears of the secretions of sputum.

The treatment of bronchial infection in patients with bronchial asthma, pulmonary emphysema, and pulmonary fibrosis is now generally initiated in our clinic by the systemic administration of antibiotics, since in a considerable portion of patients with bronchospasm, approximately 20%, increased wheezing develops after continued inhalation of penicillin and, especially, streptomycin aerosols. In patients unresponsive to systemic administration of penicillin, a program of previous bronchodilation, carried out by nebulization of 0.2 cc. of 2.25% racemic synthetic epinephrine five minutes before inhalation of penicillin aerosol, generally prevents bronchospasm and promotes expectoration of retained secretions. When antibiotic therapy has been concluded, inhalation of 0.2 cc. of nebulized 1 to 2.25% epinephrine three times daily is especially useful in cases of pulmonary emphysema, since retained

36. Barach and others.[5] Barach and others.[25] Barach and others.[28] Barach.[35m] Barach and others.[35t] Bickerman and others.[35x]

mucoid or mucopurulent secretions may be expectorated by coughing, following local bronchodilation. The use of nebulized bronchodilator solutions on arising, followed by deliberate coughing, is important in the majority of cases with bronchospasm, since otherwise mucus that accumulates in the bronchi during the night results in dyspnea during the day.

Although the dose and length of treatment with penicillin must, naturally, be modified according to the indications in the individual case, certain general principles may be mentioned. In the first place, chronic infection of the bronchial wall should be treated over a longer period than acute infection. At times, little or no improvement is manifested during the first week or 10 days in patients with severe suppurative disease. When procaine penicillin G is used by intramuscular injection in the treatment of chronic bronchitis, doses of 300,000 units a day, or 600,000 units every two days, for three to five weeks may be necessary. Adequate treatment is revealed by absence of pus from the sputum and disappearance of Gram-positive bacteria. If clinical improvement continues, the presence of Gram-negative bacteria does not indicate active infection. Addition of streptomycin may result in a swifter therapeutic response in cases of mixed infection.[35b] The secondary infections that take place in some cases after penicillin therapy [37] and after the use of streptomycin [34] will be dealt with in a subsequent discussion.

In patients with bronchiectasis the frequency of aerosol administration and the dosage depend upon whether the patient is in a hospital or is ambulatory. For hospital patients the inhalation of 100,000 units of penicillin dissolved in 1 cc. of boiled or distilled water, isotonic sodium chloride solution, or 1% phenylephrine (neo-synephrine®) hydrochloride is employed five times a day for two to three weeks, or until the purulent quality of the expectoration has been eliminated. For ambulatory patients three treatments daily with 150,000 units of penicillin may be used, or in some cases 200,000 units twice a day, with 250,000 units given by mouth at the same time. When cough and expectoration have been substantially reduced, a smaller maintenance dose may be employed, such as 150,000 units twice a day.

When production of the mist is obtained by oxygen, a flow of 8 to 10 liters per minute from a high-pressure cylinder is used. Air pumps are also now available as the power source for nebulization.[38] The hand bulb may be used with the large-jet, baffleless vaponefrin® nebulizer, which permits the aerosolization of 1 cc. of solvent in 10 minutes; greater deposition of penicillin then takes place in the larger bronchi, similar to the effect of dust penicillin. The details of technique of aerosol therapy have been recently reviewed.[39]

In some cases of bronchiectasis a course of three to five weeks' treatment may be followed by little or no evidence of infection for a considerable period thereafter, i. e., two to four months. In more advanced cases a program of frequent courses or continued daily inhalation of penicillin appears to be advantageous. For one patient under our supervision penicillin aerosol has been used almost continuously

37. Appelbaum, E., and Leff, W.: Occurrence of Superinfections During Antibiotic Therapy, J. A. M. A. **138**:119, 1948. Sommer, L. S., and Favour, C. B.: Biologic Complications of Penicillin Therapy, Am. J. Med. **7**:511, 1949.

38. An inexpensive pump has been produced by Hugh Miller & Company, 68 Sunset Rd., Bay Shore, L. I.

39. Committee on Public Health Relations, New York Academy of Medicine: Standards of Effective Administration of Inhalational Therapy, Special Article, J. A. M. A. **144**:25, 1950.

for eight years, with pronounced and maintained improvement, characterized by reduction in cough and expectoration, a striking decrease in shortness of breath on exertion, and a gain of 40 lb. (18.1 kg.) in weight. In patients of this type daily inhalation of aerosol penicillin has eliminated a state of chronic invalidism and allowed them to pursue a gainful occupation and lead a relatively normal life, with only moderate restriction in physical activity.

In cases of bronchiectasis in which pneumonitis develops owing to the presence of resistant strains of M. pyogenes var. aureus, penicillin aerosol has been demonstrated to be effective when intramuscular injection of penicillin was found valueless. In a youth of 16 years who had been treated with penicillin three times previously for sinusitis, chronic bronchitis, and bronchiectasis, widespread bilateral M. pyogenes pneumonitis developed one year later; this infection was not controlled by 1,000,000 to 4,000,000 units of penicillin administered intramuscularly over one month. The patient was then gravely ill, cyanotic, and dyspneic, and was in an oxygen tent. Systemic administration of penicillin was eliminated and replaced by inhalation of 1,000,000 units of penicillin aerosol daily; disappearance of fever and clearing of the extensive pulmonary involvement took place promptly, with complete clinical recovery two weeks later. The sputum cultures revealed disappearance of M. pyogenes var. aureus, which had been resistant to 5 units of penicillin per cubic centimeter prior to aerosol therapy.[5b] This case, as well as the cases of lung abscess described below, demonstrates the efficiency of maintaining a high local concentration of penicillin in the sputum and on the bronchial mucous membrane in infections with relatively resistant organisms.

Lung Abscess.—The treatment of lung abscess by intramuscular injection of penicillin, with or without sulfadiazine or streptomycin, has been followed by complete recovery in many instances. In five of our patients with lung abscess in whom previous treatment with intramuscular injections of penicillin, for approximately one month, was not followed by significant improvement, subsequent inhalation of penicillin aerosol without systemic treatment resulted in complete clinical recovery.[40] Penicillin aerosol in conjunction with intramuscular administration has been reported by others in the successful treatment of lung abscess.[41] It would appear likely that penicillin aerosol enters the abscess during the periods that the cavity is open; in addition, the high sputum concentrations of penicillin, between 10 and 100 units per cubic centimeter, reduce local bronchial infection and the associated pneumonitis.

The use of penicillin aerosol for at least three or four weeks is indicated in cases of both acute and chronic lung abscess and, if any improvement is then manifested, for a longer duration of treatment before resort to surgery. The addition of the sulfonamides or streptomycin, either intramuscularly or as an aerosol, is justified in those cases in which Gram-negative organisms are found on sputum culture. Terramycin, chloramphenicol, and aureomycin are so effective that they are now generally used to eliminate Klebsiella pneumoniae, as will be discussed below.

Acute and Chronic Sinusitis.—The treatment of both acute and chronic infectious sinusitis by nasal inhalation of penicillin aerosol, in conjunction with repeated production of a partial vacuum in the nasal passages, appears to be one of the valuable

40. Garthwaite and Barach.[5b] Bickerman and others.[35x]

41. Segal and others.[35d] Christie, H. E.; Aronovitch, M., and Meakin, J. F.: Aerosol Therapy for Lung Abscess, Canad. M. A. J. **62**:478, 1950.

uses of antibiotic aerosols.[42] Introduction of penicillin to the sinuses by this method has been shown to be a practical therapeutic procedure in the majority of cases of chronic, as well as acute, sinusitis. Negative pressure, produced either by the passage of air through a Venturi tube or by a rubber bulb, accomplishes ventilation of the sinuses and, in some cases, drainage of the retained secretions; in addition, release of the partial vacuum in the nasal passages is responsible for introduction of penicillin into the sinus cavities themselves. Although in a number of cases of acute sinusitis the condition may be satisfactorily treated by a daily inhalation, the administration of penicillin with negative pressure is more apt to yield better results when it is carried out two, or preferably three, times a day.

Culture of the sputum or of the nasal secretions, as well as a smear for the demonstration of pus cells, or eosinophiles, is carried out preferably before and during the treatment as a guide to the adequacy of the dose administered.

In many cases of acute sinusitis, as is well known, recovery occurs without specific therapy. In other instances, however, the condition assumes a subacute form, which may be accompanied by persistent coughing, apparently related to a postnasal drip. The employment of penicillin aerosol with negative pressure offers a practical method of obtaining prompt recovery by providing aeration, drainage, and introduction of penicillin in the majority of infected sinuses of this type. The disappearance of the associated cough in these cases is generally striking, even after three to four days' treatment. In 36 of 40 patients with acute sinusitis, and 103 of 150 patients with chronic sinusitis, significant improvement took place after administration of aerosol penicillin with negative pressure (Table 1).[28]

Recovery from chronic purulent sinusitis has been achieved by this procedure in many cases in which routine methods have failed. Our studies with penicillin aerosol, inhaled in conjunction with negative pressure, in both children and adults, indicate that clinical recovery from persistent chronic infectious sinusitis may now be expected in the majority of cases in which the infecting organism is of the Gram-positive type.

In cases of acute sinusitis 100,000 units of penicillin dissolved in 1 cc. of 1% ephedrine sulfate or 1% phenylephrine hydrochloride may be administered one to three times a day for 5 to 10 days. In chronic sinusitis 100,000 units may be used three to four times a day for two to four weeks. The details of the techniques of aerosol therapy used in our studies have been recently reviewed.[43]

COMPARATIVE EFFECTIVENESS OF AEROSOL AND DUST PENICILLIN

The blood levels after inhalation of 50,000 and of 200,000 units of penicillin aerosol are shown in Chart 1. It will be seen that after inhalation of 200,000 units of penicillin aerosol a blood level of 0.83 unit per cubic centimeter is obtained after the first half-hour and that this decreases in five hours to an average blood level of 0.02 unit per cubic centimeter. After inhalation of 50,000 units a blood level of 0.2 unit per cubic centimeter was obtained one-half hour after the inhalation. In 150

42. Footnotes 28 and 29. Eastlake.[35a']

43. Eastlake.[35a'] Barach, A. L.; Garthwaite, B., and Soroka, M.: For the Inhalation of Penicillin Aerosol, Mod. Hosp. **66**:100, 1946. Segal, M. S.; Levinson, L., and Beackey, J. F.: Demand Valve for the Administration of Aerosols of Penicillin and Streptomycin, Dis. Chest **14**:386, 1948.

blood-level determinations after routine inhalation of 50,000 units of penicillin the average concentration was found to be 0.08 unit per cubic centimeter in one-half hour and 0.04 unit per cubic centimeter in two hours. The differences in cooperation and intelligence of the patient are in part responsible for the variation in the amount of penicillin deposited in the lungs.

The inhalation of powdered or micronized penicillin has been advocated by Taplin and associates [44] and Krasno and their co-workers.[45] Contrary to their reports, irritation of the tongue and throat has been found more frequently in our experience with inhalation of powdered penicillin than with use of the aerosol solution. This type of complication can be lessened in some patients by drinking a glass of water during the treatment. Severe bronchospasm has resulted more frequently after inhalation of micronized penicillin than after that of aerosol penicillin, but, as pointed out above, penicillin by injection is generally indicated in cases with

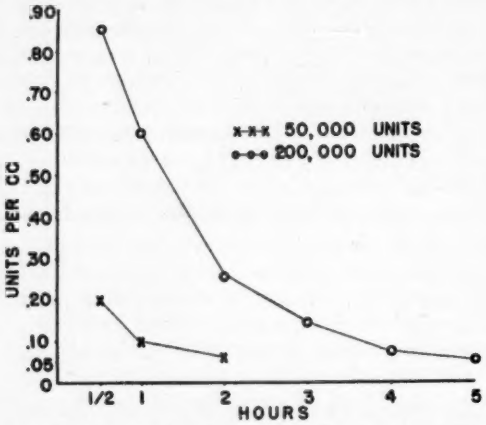

Chart 1.—Blood levels following 50,000 and 200,000 units of penicillin aerosol (200,000 units expelled through apparatus prior to tests with 200,000 units).

bronchospasm, i. e., bronchial asthma and pulmonary emphysema, in preference to either aerosol or dust medication.

The prolonged high blood levels reported by Krasno and colleagues have not been found in our studies after inhalation of micronized penicillin. In fact, inhalation of dust penicillin results in blood levels much lower than those obtained after inhalation of penicillin aerosol. In Chart 2 it will be seen that blood levels after inhalation of 100,000 units of micronized penicillin are of the order of 0.02 to 0.04 unit per cubic centimeter, persisting only for three hours, and after inhalation of 200,000

44. Taplin, G. C., and Bryan, L.: Administration of Micronized Therapeutic Agents by Inhalation of Topical Application, Science **105**:502, 1947. Taplin, G.; Cohen, S., and Mahoney, E.: Prevention of Postoperative Pulmonary Infections: Inhalation of Micropowdered Penicillin and Streptomycin, J. A. M. A. **138**:41, 1948.

45. Krasno, L.; Karp, M., and Rhodes, P.: (*a*) Inhalation of Penicillin Dust, Science **106**:449, 1947; (*b*) Inhalation of Penicillin Dust, Ann. Int. Med. **28**:607, 1948; (*c*) Inhalation of Penicillin Dust, J. A. M. A. **138**:344, 1948.

units, 0.25 unit per cubic centimeter after the first half-hour then sharply falling between the second and the fifth hour to 0.06 to 0.01 unit per cubic centimeter. These results were based on the use of the Hobby dilution method,[46] with a hemolytic Streptococcus as the standard organism. Krasno and associates [45a,b] reported that blood levels of 0.03 to 1.92 unit per cubic centimeter were obtained frequently after inhalation of 100,000 units, these levels declining slowly over the next four hours, findings which we have been unable to confirm.

In Chart 3 the blood level after inhalation of 200,000 units of penicillin in micronized form is compared with that after inhalation of the same amount as an aerosol,

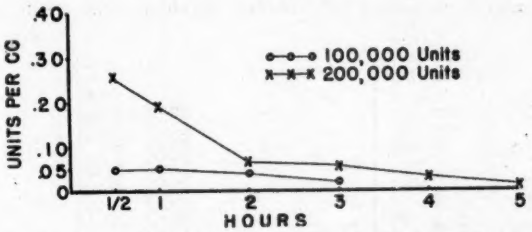

Chart 2.—Blood levels following inhalation of micronized penicillin in dosages of 100,000 and 200,000 units with the Abbott "aerohaler" (200,000 units expelled through apparatus prior to tests with 200,000 units).

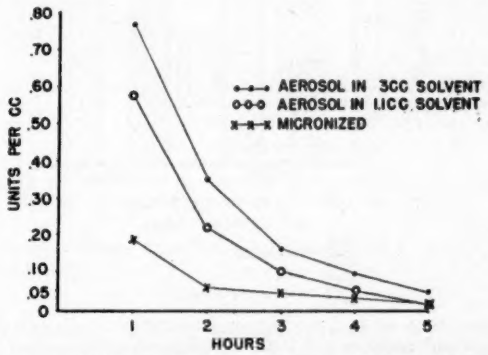

Chart 3.—Blood levels following inhalation of 200,000 units of micronized penicillin, 200,000 units of penicillin aerosol in a total of 1.1 cc. of 5% alcohol and 200,000 units of penicillin aerosol in 3 cc. of distilled water (seven tests on the same five patients with each method).

the latter (*a*) in a small volume of diluent, 1.1 cc., and (*b*) in a larger volume of diluent, 3 cc. It will be seen that the blood levels with both the small and the large volume of diluent are far higher with the aerosol technique than those obtained with micronized penicillin. Furthermore, these results were obtained after expelling 200,000 units through the aerohaler and leaving the residue in it before an additional 200,000 units of penicillin was added. This was done to simulate the conditions

46. Hobby, G. L.; Meyer, K., and Chaffee, E.: Activity of Penicillin in Vitro, Proc. Soc. Exper. Biol. & Med. **50**:277, 1942.

which would exist after the first treatment, but it is responsible for a higher blood level than would have occurred with a test without the residue added.

A swift nebulization of penicillin aerosol, comparable with the time required for micronized penicillin, may also be obtained with a nebulizer that produces particles of large size, such as the baffleless vaponefrin® nebulizer. In Chart 4 it will be seen that high sputum levels of penicillin are found with both the baffleless nebulizer and with micronized penicillin, after inhalation of 100,000 and 200,000 units, i. e., from 300 to 1,100 units of penicillin per cubic centimeter of sputum. In this instance the sputum was collected for four hours after nebulization. Mists of large particle size are especially suitable for treatment of sinusitis and infections of the nasopharynx but may be employed for bronchial infections, with results comparable to

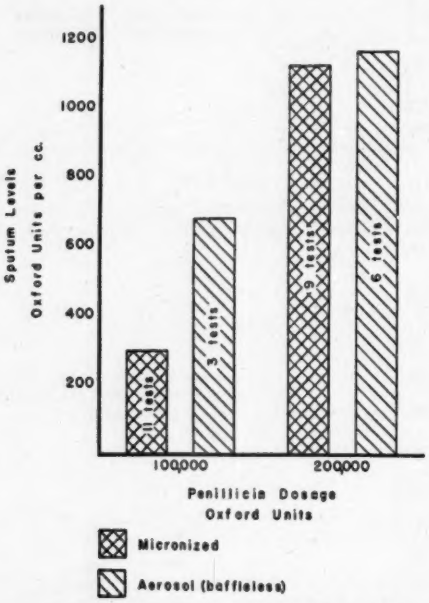

Chart 4.—Sputum levels of penicillin following inhalation of penicillin through the large-jet baffleless vaponefrin® nebulizer and following inhalation of micronized penicillin, in doses of 100,000 and 200,000 units of penicillin at a single inhalation.

those found after administration of dust penicillin. Simplicity of administration is, in fact, the only advantage discernible in the use of micronized penicillin. The dust cartridges are more costly than aerosol tablets per unit of penicillin and therefore impractical for long-continued use with patients of moderate means. Our appraisal of its clinical value will be presented briefly.

The inhalation of penicillin dust was studied in a group of 40 patients with bronchiectasis and chronic bronchitis. Twenty-five patients received micronized penicillin in a dose ranging from 200,000 to 400,000 units a day. The remaining 15 patients received combined penicillin and streptomycin dust inhalations, the daily dose of which ranged from 200,000 units of penicillin and 0.2 gm. of streptomycin

to 400,000 units of penicillin and 0.4 gm. of streptomycin. The duration of treatment varied from 4 to 150 days. In several instances in which clinical relapse occurred additional courses of therapy were employed. Of a total of 30 courses of penicillin dust therapy, satisfactory improvement took place in 21, manifested by reduction

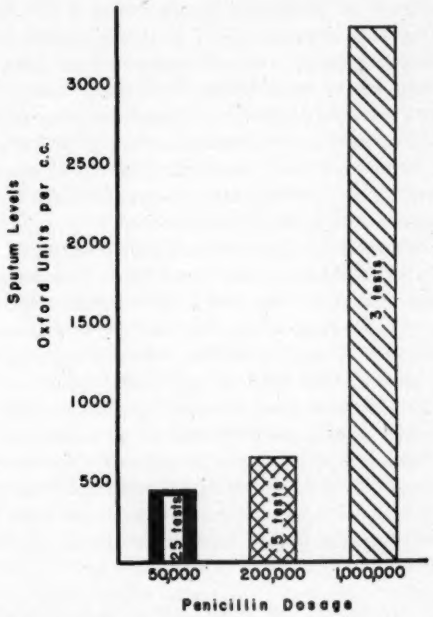

Chart 5.—Average sputum levels of penicillin after inhalation of 50,000, 200,000, and 1,000,000 units of penicillin aerosol administered as a single inhalation.

TABLE 2.—*Results of Antibiotic Dust Therapy in Bronchiectasis and Chronic Bronchitis*

Drug Employed	No. of Cases	Daily Dose	Duration of Courses, Days	Total No. of Courses	Improvement Following Individual Courses	
					Satisfactory	Slight or None
Penicillin	25	200,000 to 400,000 units	3-140	30	21	9
Combined penicillin and streptomycin	15	200,000 to 400,000 units — 0.2 to 0.4 gm.	7-63	20	13	7

in cough, sputum, and bacterial infection, as evidenced by the disappearance of Gram-positive organisms on culture and elimination or decrease of pus cells in the sputum. Of 20 courses of combined penicillin and streptomycin dust inhalations, a satisfactory response took place in 13, as seen in Table 2.

In an analysis of the bacteriologic data, the effect of antibiotic-dust inhalations on sputum cultures was found to be as follows: Of 21 courses of penicillin-dust

therapy, the sputum showed no pyogenic organisms on culture in 3 instances, K. pneumoniae in 7, and Gram-negative bacteria of the Esch. coli, Aerobacter aerogenes, or Ps. aeruginosa group in 10 (Table 3). In 13 of 21 cultures of the expectoration after penicillin-dust inhalations, Gram-negative bacilli of the Esch. coli and A. aerogenes group were found, results which are similar to those originally reported after aerosol penicillin.[5a] In one case, a Streptococcus of the viridans group, which had been the predominant organism prior to therapy, continued to grow out on culture after treatment. After 21 courses of combined penicillin- and streptomycin-dust inhalations, members of the coliform, P. vulgaris, and A. aerogenes families were recovered in 12 cases, and either no organism or yeast cells in 6 cases; of the 3 remaining cases cultures revealed K. pneumoniae and M. pyogenes var. aureus in 1, Esch. coli and pneumococci in 1, and Esch. coli and K. pneumoniae in 1. Persistence of members of the coliform and A. aerogenes group was found, despite the addition of streptomycin to the penicillin dust.

Adverse reactions to the inhalation of antibiotic dust included sore, red tongue; red, edematous pharynx, and pronounced increase in bronchospasm. Five patients given penicillin-dust inhalation were forced to discontinue therapy because of one or more local reactions. A similar number of patients were compelled to discontinue combined penicillin- and streptomycin-dust inhalation therapy. The addition of streptomycin dust increased the severity of bronchospasm.

In a series of 25 additional cases observed in office practice, the clinical results with inhalation of dust penicillin were similar to those described above. A dose of 400,000 units daily was generally required for marked reduction of infection in most cases of bronchiectasis. In some cases 600,000 units daily was employed to convert purulent sputum to mucoid expectoration. A comparable dose of penicillin administered as an aerosol appeared to give a better therapeutic response, with fewer and less severe reactions.

COMMENT ON PENICILLIN INHALATION

The value of penicillin by inhalation depends on local deposition of a therapeutic drug in relatively high concentration in the respiratory tract. The effect of systemic administration of drugs, either orally or parenterally, is dependent upon an intact blood supply to the involved tissues, since the drugs are not secreted into the bronchi, except in lobar pneumonia. In certain parts of the body not efficiently provided with circulating blood to the diseased area, topical application of therapeutic substances is required to overcome infection. Examples of this state of affairs occur in the brain, the eye, the pleural cavity, the accessory nasal sinuses, and, in similar circumstances, the bronchi and lungs. Ample evidence is available to indicate that intramuscular injection of penicillin does not alter the course of Pneumococcus empyema, whereas 30,000 units injected into the pleural cavity for two or three doses will frequently result in elimination of the infection. In our experience, the intramuscular injection of penicillin has not been effective in the treatment of subacute and chronic sinusitis in cases in which subsequent use of aerosol penicillin, in conjunction with negative pressure, has produced striking improvement or cure. Similarly, cases of lung abscess have been observed in which prolonged intramuscular injection of penicillin did not alter the course of the disease but subsequent administration of aerosol penicillin in effective doses was followed by clinical recovery.

Chronic bronchial infections, especially bronchiectasis, have been notoriously resistant to conventional methods of treatment. Although patients with bronchiectasis have been favorably influenced by intramuscular injection of penicillin, the degree of benefit is generally considerably less than that produced by inhalation of penicillin, especially when nebulized bronchodilator solutions have been employed prior to treatment to relieve bronchospasm and aid in the expectoration of retained purulent or mucopurulent exudate.

In lobar pneumonia, the intramuscular injection of penicillin is followed by a substantial level of penicillin in the expectoration. In this condition, the barrier between the alveoli and the blood stream is broken down and the penicillin present in the blood is delivered to the site of the infection. However, in chronic bronchitis, bronchiectasis, lung abscess, and other types of acute and chronic bronchopulmonary infections, the intramuscular injection of penicillin is not accompanied, generally, by the appearance of demonstrable levels of penicillin in the expectoration. In contrast, the inhalation of penicillin as an aerosol, or as a powder, is followed by high levels of penicillin in the expectoration, from 50 to 2,000 units of penicillin per cubic centimeter of sputum, depending upon the dose. Similarly, streptomycin is not present in the sputum in most instances after intramuscular injection, whereas high concentrations are found in the expectoration after inhalation as an aerosol.

In a comparative study by Laurent, McIlroy, and Hadley,[47] the concentration of penicillin in washed lung extracts was 60 times as high one hour after aerosol administration as that found after intramuscular injection of a similar dose. Similar, although less striking, findings were reported after inhalation of streptomycin aerosol, as compared with intramuscular injection of this drug.

In the study of Wilson and co-workers,[48] a comparison of inhalation and injection therapy of penicillin in experimental pneumonia revealed that the inhalation of penicillin aerosol was as effective as, and, in some cases more effective than, a comparable dose given by intramuscular injection. The demonstration by Segal [35d] that Pneumococcus lobar pneumonia was cured by the inhalation of penicillin may be interpreted as an effect of absorption of small amounts of the drug into the blood stream, as well as of local deposition of penicillin.

In the treatment of chronic bronchopulmonary infection, the problem of bacterial resistance is of major importance. Although neither the β-hemolytic nor the viridans type of Streptococcus appear as resistant organisms after penicillin treatment, M. pyogenes var. aureus has been frequently reported as a resistant strain. The high local (sputum) concentrations of penicillin produced by aerosol administration make possible the elimination of resistant strains of this organism from the respiratory tract in many instances. Sherris and Florey [49] found that most strains of M. pyogenes var. aureus from deep-seated infections were penicillin-sensitive, and that the resistant strains were mostly from superficial lesions and less likely to be

47. Laurent, A. M.; McIlroy, A. P., and Hadley, F. P.: Penicillin and Streptomycin in Lungs and Blood Serum of Rats Following Inhalational and Intramuscular Administration, Proc. Soc. Exper. Biol. & Med. **68**:213, 1948.

48. Wilson, C. E.; Hammond, C. W.; Byrne, A. F., and Bliss, E. A.: Control of Experimental Pneumonia with Penicillin: Comparison of Inhalation and Injection Therapy, Bull. Johns Hopkins Hosp. **77**:411, 1945.

49. Sherris, J. C., and Florey, M. E.: Relation of Penicillin Sensitivity in Staphylococci to Clinical Manifestations of Infection, Lancet **1**:309; **2**:10, 1951.

associated with signs of inflammation or suppuration. Bacitracin may now be given by intramuscular injection for the treatment of resistant strains of M. pyogenes var. aureus, since it has been shown to be effective in such conditions as metastatic lung abscess due to the organism.[50] Although in most patients the presence of albumin and casts in the urine develops during its use, this nephrotoxicity of bacitracin should not contraindicate its use in serious, intractable infections.[51] Other methods of combating bacterial resistance will be discussed in the presentation of the results of therapy with the newer antibiotic drugs.

II. Aureomycin, Terramycin, and Chloramphenicol

The broad range of antimicrobial activity of the newer antibiotic agents has stimulated the use of these drugs in a wide variety of disease of bacterial, viral, and rickettsial origin. In the preceding section, Part I, an appraisal was made of the value of penicillin, chiefly as administered by inhalation, in treatment of chronic diseases of the respiratory tract. During the past two years a comparative study has been carried out on the use of aureomycin, chloramphenicol, and terramycin in treatment of bronchiectasis and chronic bronchitis, frequently in patients with the associated clinical entities of bronchial asthma and pulmonary emphysema. The broad-spectrum antibiotics have similar, although not identical, antibiotic activity, but all of them, aureomycin, chloramphenicol, and terramycin, produce a striking inhibition of growth of Gram-positive and of most Gram-negative micro-organisms and are effective after oral administration. These therapeutic considerations appeared to be important, since penicillin and streptomycin aerosols at times increased bronchospasm in patients whose bronchopulmonary infection was associated with asthma or pulmonary emphysema.

Since the introduction of aureomycin, an extensive literature has accumulated on the clinical effectiveness of these three antibiotics in acute respiratory infections. Bacterial pneumonias due to a wide variety of organisms, including the Pneumococcus, the hemolytic Streptococcus, hemolytic M. pyogenes var. aureus, and K. pneumoniae, have shown striking improvement, clinically and bacteriologically, during therapy with the broad-spectrum antibiotics.[52] The therapeutic response of

50. Meleney, F. L.; Longacre, A. B.; Altemeier, W. A.; Reisner, E. H., Jr.; Pulaski, E. J., and Zintel, H. A.: Efficacy and Safety of the Intramuscular Administration of Bacitracin in Various Types of Surgical and Certain Medical Infections, Surg., Gynec. & Obst. **89**:657, 1949.

51. Reisner, E. H., Jr.; Bailey, F. N., and Appelbaum, E.: Treatment of Pneumonia with Bacitracin, Ann. Int. Med. **34**:1232, 1951. Prigal, S. J., and Furman, M. L.: Use of Bacitracin, a New Antibiotic, in Aerosol Form: Preliminary Observations, Ann. Allergy **7**:662, 1949.

52. (*a*) Collins, H. S.; Paine, T. F., Jr., and Finland, M.: Clinical Studies with Aureomycin, Ann. New York Acad. Sc. **51**:231, 1948. (*b*) Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: The Pharmacology and Clinical Trial of Aureomycin: A Preliminary Report, ibid. **51**:267, 1948. (*c*) Chandler, C. A.; Schoenbach, E. B., and Bryer, M. S.: Observations on Staphylococcal Infections Treated with Aureomycin, Pediatrics **4**:149, 1949. (*d*) Recinos, A., Jr.; Ross, S.; Olshaker, B., and Twible, E.: Chloromycetin in the Treatment of Pneumonia in Infants and Children, New England J. Med. **241**:733, 1949. (*e*) Gruber, S.; Turin, R. D.; Sternberg, S. D., and Rascoff, H.: Friedländer's Pneumonia with Multiple Lung Abscesses: Recovery Following the Use of Streptomycin and Aureomycin, J. Pediat. **36**:237, 1950. (*f*) Olshaker, B.; Ross, S.; Recinos, A., and Twible, E.: Clinical Evaluation of Aureomycin and Chloramphenicol in Pneumonia in Infants and Children, J. Clin. Invest. **28**:1049, 1949. (*g*) Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Terramycin in the Treatment of Pneumococcic

atypical or viral pneumonia and the "unclassified" pneumonias was similarly gratifying.[53] Herrell, Heilman, and Wellman [54] reported a satisfactory clinical response with terramycin in 10 patients with a variety of respiratory infections, including acute pharyngitis and tonsillitis due to beta-hemolytic Streptococcus, laryngotracheobronchitis due to Hemophilus influenzae, and severe infection of the upper respiratory tract of undetermined origin. Caldwell and associates [53i] noted improvement in three patients with nonspecific tracheobronchitis within 24 to 48 hours after the beginning of terramycin therapy. Finland and his co-workers [53b] mentioned equally beneficial results of aureomycin in 18 patients with bronchopulmonary disease due to the influenza A virus. It is noteworthy that both Finland and Kirby [55] found it impossible to determine definitely whether the response resulted from the suppression of the infecting virus or that of secondary bacterial invaders, since aureomycin has failed to influence experimental infections due to the influenza virus.

The few reports on therapy of lung abscess similarly reflect the improvement which may be expected with these antibiotics. Chandler, Schoenbach, and Bryer [52c] reported the case of an infant with multiple lung abscesses due to hemolytic M. pyogenes var. aureus who improved under aureomycin therapy, after penicillin, streptomycin, and sulfonamides had been used without altering the course of the infection. Another infant with a K. pneumoniae infection of the lungs and multiple cavities, cited by Gruber and associates,[52e] had an impressive response to a combination of aureomycin and streptomycin, with sterilization of the sputum and closure of all cavities. King and his group [56] demonstrated the beneficial effect of terramycin on two patients with lung abscess, which showed x-ray evidence of healing after failure to heal with penicillin and sulfonamide.

Chronic pulmonary suppuration was not found to respond in as striking a manner as the acute bacterial infections of the respiratory tract. Collins, Gocke, and Finland [57] treated 20 patients with aureomycin during an exacerbation of the chronic underlying bronchopulmonary infection. Most of their patients presented evidence, both clinically and roentgenographically, of long-standing chronic bronchitis and

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and Other Bacterial Infections, Ann. New York Acad. Sc. **53**:433, 1950. (*h*) Timpanelli, A.; Huebner, R. D., and McDermott, W.: Terramycin in the Treatment of Pneumococcal and Mixed Bacterial Pneumonias, ibid. **53**:440, 1950. (*i*) Caldwell, E. R., Jr.; Spies, H. W.; Wolfe, C. K.; Lepper, M. H., and Dowling, H. F.: The Treatment of Various Infections with Terramycin, J. Lab. & Clin. Med. **36**:747, 1950. (*j*) Kneeland, Y., Jr.; Rose, H. M.; Melcher, G. W., and Price, K. M.: Experimental and Clinical Studies of Terramycin, Tr. A. Am. Physicians **63**:126, 1950.

53. (*a*) Kneeland, Y., Jr., and Melcher, G. W.: Terramycin in the Treatment of Primary Atypical Pneumonia, Ann. New York Acad. Sc. **53**:437, 1950. (*b*) Finland, M.; Wells, E. B.; Collins, H. S., and Gocke, T. M.: Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections With or Without Pneumonia, Am. J. Med. **8**:21, 1950. (*c*) Herrell, W. E.: Observations on the Clinical Use of Aureomycin, Proc. Staff Meet., Mayo Clin. **24**:612, 1949.

54. Herrell, W. E.; Heilman, F. R., and Wellman, W. E.: Some Bacteriologic, Pharmacologic, and Clinical Observations on Terramycin, Ann. New York Acad. Sc. **53**:448, 1950.

55. Kirby, W. M. M.: Recent Trends in Antibiotic Therapy, J. A. M. A. **144**:233, 1950.

56. King, E. Q.; Lewis, C. N.; Welch, H.; Clark, E. A., Jr.; Johnson, J. B.; Lyons, J. B.; Scott, R. B., and Cornely, P. B.: Clinical Observations on the Use of Terramycin Hydrochloride, J. A. M. A. **143**:1, 1950.

57. Collins, H. S.; Gocke, T. M., and Finland, M.: Aureomycin Therapy of Nonpneumococcic and Nontuberculous Bacterial Pulmonary Infections, Arch. Int. Med. **84**:875, 1949.

bronchiectasis. The bacterial flora of the sputum varied considerably, with coagulase-positive strains of hemolytic M. pyogenes var. aureus predominating. These organisms were sensitive to aureomycin but highly resistant to penicillin. Of the other organisms isolated, hemolytic streptococci, H. influenzae, and K. pneumoniae were moderately sensitive to aureomycin, while P. vulgaris, Ps. aeruginosa, and A. aerogenes proved to be resistant. Most of their patients showed some improvement, with decline in temperature, decrease in cough and amount of sputum, and a change from a purulent to a mucoid sputum. The susceptible strains of bacteria were cleared rapidly from the sputum, only to be replaced in the majority of cases by the above-mentioned resistant organisms. In a series of 34 patients treated for pneumonia with terramycin reported by Timpanelli, Huebner, and McDermott,[52h] 2 failed to respond satisfactorily, and further investigation disclosed that the acute pneumonia was superimposed on chronic bronchiectasis in one case and on pulmonary fibrosis in the other.

Hewitt and Williams [58] employed chloramphenicol for 11 patients with chronic pulmonary disease, including bronchiectasis, chronic bronchitis, asthma, and emphysema. The bacterial flora of the sputum seems to have been in large part Gram-negative, since most of their patients had received penicillin with little or no benefit. Six patients had prompt subsidence of symptoms, including cough and expectoration, within 48 hours, with disappearance of the Gram-negative bacilli. One patient with a resistant strain of M. pyogenes var. aureus showed no improvement, while four patients who presented chronic infection without acute exacerbation failed to benefit, as judged by cough or character of the sputum. Both clinical and bacteriological results were significantly poorer in cases of chronic than in cases of acute infections, and the relapse rate was higher in the former. In another report, by Finland and his group,[59] five patients with miscellaneous infections of the respiratory tract due to mixed organisms showed no appreciable effect from terramycin. In a discussion, Barach [60] stated that 40 patients with chronic infections of the respiratory tract treated with terramycin showed favorable clinical results. A comprehensive report by Schwachman and associates [61] on aureomycin therapy in mucoviscidosis with pulmonary fibrosis indicated that an excellent response took place in 31 of 35 cases, with disappearance of cough, improvement in general well-being, increased appetite, and gain in weight. Hemolytic M. pyogenes var. aureus was the predominating organism in all cases. Clinical improvement bore no relation to bacteriological improvement, the former being commonly and the latter only rarely observed. In most cases of extensive pulmonary involvement relapse occurred when administration of aureomycin was discontinued. On the whole, most of the reports on the treatment of chronic pulmonary infections with the broad-spectrum antibiotics emphasize the variability of response. Although permanent improvement was not

58. Hewitt, W. L., and Williams, B., Jr.: Chloromycetin (Chloramphenicol) in the Treatment of Infections, New England J. Med. **242**:119, 1950.

59. Finland, M.; Gocke, T. M.; Jackson, G. G.; Womack, C. R., and Kass, E. H.: Clinical Studies on Terramycin, Ann. New York Acad. Sc. **53**:290, 1950.

60. Barach, A. L.: Discussion of Kneeland's Paper, "Experimental and Clinical Studies of Terramycin," Tr. A. Am. Physicians **63**:126, 1950.

61. Schwachman, H.; Crocker, A. C.; Foley, G. E., and Patterson, P. R.: Aureomycin Therapy in Pulmonary Involvement of Pancreatic Fibrosis (Mucoviscidosis), New England J. Med. **241**:185, 1949.

reported, a favorable effect was evident clinically, especially in patients suffering from an acute exacerbation of their underlying disease. The amount of benefit derived in the individual cases appeared to depend largely "on the nature of the offending organisms, their susceptibility to the antibiotic and the extent and character of the pulmonary lesions." [57] The demonstrated fact that Gram-negative as well as Gram-positive organisms were susceptible to these broad-spectrum antibiotics suggested that a therapeutic effect might be achieved in chronic pulmonary infections superior to that obtained with the administration of penicillin.

METHODS OF INVESTIGATION

Of 76 patients, 31 with bronchiectasis and 45 with chronic bronchitis associated with bronchial asthma and pulmonary emphysema were given one or more courses of aureomycin, terramycin, or chloramphenicol. The dosage in this series, irrespective of the drug employed, was maintained at 2 gm. daily for a period of three or four days, followed by 1.5 gm. for an additional two or more days, prescribed in four equal doses daily. The average duration of therapy for the two groups extended over a period of five to seven days, with the total dose varying from 6 to 30 gm., with an average of 10.7 gm. Six additional patients, discussed later, were maintained on mixed broad-spectrum antibiotic therapy for more than one week.

Most of the patients selected for this study had been followed for several years, and clinical trial with sulfonamides, penicillin, and streptomycin, and combinations of these drugs had yielded temporary benefit, without permanent arrest of their infection. However, instances of clinical cure of chronic bronchitis, i. e., freedom from symptoms of cough or expectoration for three years or more, have been observed as a result of penicillin treatment, chiefly by inhalation, as illustrated by Case 1 in the Addendum. In this series, one or more courses of broad-spectrum antibiotic therapy were administered for an acute exacerbation of an underlying infection, either spontaneous or initiated by acute viral disease, as well as for the chronic bronchial infection itself. The majority of patients, therefore, were ambulatory and afebrile at the time treatment was begun. Improvement was evaluated in terms of cough, character and amount of expectoration, and results of bacteriological study of the sputum before and after therapy. In addition, such factors as gain in weight, increase in appetite, reduction in number of asthmatic attacks, and relief from dyspnea were considered in the final appraisal. In a number of cases two to five courses of therapy (150 in all) were given to individual patients, the same or another antibiotic being employed. Determination of the sensitivity of the infecting organisms to the drugs employed was carried out in selected subjects. Clinical and bacteriological data on 76 patients are presented in Tables 4, 5, and 6. Case histories of six patients in this series and of seven additional patients are reported in detail at the end of the paper.

RESULTS

The individual responses in patients with bronchiectasis are presented in Table 4. Of 31 subjects treated with one or another of the three broad-spectrum antibiotics, 26 exhibited moderate to pronounced improvement—9 with aureomycin, 6 with terramycin, and 11 with chloramphenicol, as judged by cough, expectoration, and clinical well-being. Of 45 patients with chronic bronchitis associated with bronchial asthma or pulmonary emphysema, marked or moderate benefit took place in 37—10 with aureomycin, 10 with terramycin, and 17 with chloramphenicol (Tables 5 and 6). Of the combined series of 76 patients with chronic bronchopulmonary infection, 63 showed pronounced or moderate clinical improvement, with corresponding evidence of diminished infection presented by sputum, smear, and culture. No statistical studies on the effect produced by any individual antibiotic were attempted in this series.

Of 45 sputum specimens assayed for antibiotic activity after administration of 500 mg. of terramycin, aureomycin, or chloramphenicol, a trace of the drug,

TABLE 4.—*Effect of Aureomycin, Terramycin and Chloramphenicol in Bronchiectasis*

Case No.	Sputum Smear and Culture		Drug	Dose, Gm.	Comment
	Before	After			
1	Moderate pus cells; eosinophiles; M. pyogenes aureus; hemolytic Streptococcus	Occasional eosinophiles; no pus cells; few colonies of M. pyogenes aureus	Aureomycin	10	Marked improvement in cough and sputum
2	Str. viridans; H. influenzae; many pus cells	N. catarrhalis; no pus cells	Aureomycin	17	Cough and sputum eliminated
3	Purulent sputum; M. pyogenes aureus; K. pneumoniae	Few pus cells; Str. viridans	Aureomycin	12	Slight decrease in cough and sputum
4	Purulent sputum; Esch. coli; P. vulgaris	Moderate pus cells; Esch. coli; P. vulgaris	Aureomycin	8	Moderate decrease in cough and sputum
5	Moderate pus cells; M. pyogenes aureus; hemolytic Streptococcus	Occasional pus cells; sterile culture	Aureomycin	10	Cough disappeared; clinical improvement
6	Many pus cells; Str. viridans; M. pyogenes aureus	Few pus cells; A. aerogenes	Aureomycin	16.5	Marked improvement; no sputum; cough reduced
7	Moderate pus cells; Str. viridans	Few pus cells; Str. viridans	Aureomycin	8	Slight improvement
8	Moderate no. pus cells; Str. viridans; K. pneumoniae	Few pus cells; hemolytic Streptococci	Aureomycin	6	Marked improvement
9	Many pus cells; K. pneumoniae	Few pus cells; K. pneumoniae	Aureomycin	9	Moderate improvement
10	Many pus cells; N. catarrhalis; Str. viridans	Occasional pus cell; M. pyogenes aureus; hemolytic Streptococci	Aureomycin	8	Sputum and cough decreased
11	Moderate pus cells; Str. viridans; Esch. coli	Moderate no. pus cells; few eosinophiles; sterile	Aureomycin	10	Moderate improvement in cough and breathing; sputum decreased
12	Moderate no. of pus cells; pneumococci; hemolytic streptococci	No pus; sterile	Terramycin	10	Slight improvement
13	Ps. aeruginosa; K. pneumoniae	Ps. aeruginosa	Terramycin	17.0	Less cough, dyspnea, and sputum
14	Viridans streptococci; N. influenzae; N. catarrhalis; many pus cells	N. catarrhalis; no pus cells	Terramycin	7	Marked improvement; no asthma or cough
15	Moderate no. of pus cells; hemolytic Streptococci; M. pyogenes aureus	Occasional pus cells; sterile	Terramycin	15	Cough disappeared
16	Purulent sputum; M. pyogenes aureus	Few pus cells; viridans Streptococci	Terramycin	12	Moderate decrease in cough and expectoration
17	M. pyogenes aureus; Str. viridans	Few pus cells; C. albicans	Terramycin	20	Dyspnea markedly relieved
18	M. pyogenes aureus; Str. viridans	Few pus cells; P. vulgaris	Terramycin	14	Marked decrease in cough and sputum
19	P. vulgaris; Esch. coli	Many pus cells; P. vulgaris	Chloramphenicol	28	Reduction in sputum and cough
20	Moderate pus cells; hemolytic streptococci	Few pus cells; P. vulgaris	Chloramphenicol	8	No improvement
21	Few pus cells; sterile	Str. viridans predominant	Chloramphenicol	8	No improvement
22	Moderate no. of pus cells; Str. viridans; K. pneumoniae	Few pus cells; hemolytic Streptococci	Chloramphenicol	8	Marked improvement in cough; less sputum
23	Moderate pus cells; K. pneumoniae	No pus cells; occasional K. pneumoniae	Chloramphenicol	15	Sputum and cough almost gone
24	Many pus cells; Pneumococcus; K. pneumoniae	No pus cells; Gram-negative diplococci	Chloramphenicol	8	Marked improvement in cough and dyspnea; no pus in sputum
25	Moderate pus cells; M. pyogenes aureus; Str. viridans; few pus cells and eosinophiles; C. albicans	Moderate pus cells; Pneumococcus	Chloramphenicol	12	Cough decreased; sputum white
26	Many pus cells	Occasional pus cell	Chloramphenicol	10	Cough and sputum diminished
27	Many pus cells; occasional eosinophile; K. pneumoniae; M. pyogenes aureus	No pus cells; occasional K. pneumoniae	Chloramphenicol	8	Moderate improvement in sputum and cough
28	Moderate no. of pus cells; A. aerogenes	Few pus cells; N. catarrhalis; Str. viridans	Chloramphenicol	8	Less cough and sputum
29	Few pus cells; viridans type of Streptococci	Few pus cells	Chloramphenicol	8	Moderate improvement
30	Many pus cells; Ps. aeruginosa; Str. viridans	Few pus cells; diphtheroids	Chloramphenicol	8	Moderate improvement; sputum diminished
31	Moderate no. of pus cells; pneumococci; K. pneumoniae	Few pus cells	Chloramphenicol	12	Marked improvement; sputum white; cough decreased

between 1 and 2 γ per cubic centimeter of sputum, was found in 30. In addition, a patient with chronic sinusitis was given a single dose of 750 mg. of terramycin, and the antral washing, consisting of 5 cc. of saline, four hours later revealed the presence of terramycin in a concentration of 2 γ per cubic centimeter of antral washing.

An analysis of the bacteriological data following therapy with the broad-spectrum antibiotics is of interest. A review of our previous studies with parenteral administration of penicillin, and with use of aerosol and dust penicillin [62] showed that the sputum was negative for Gram-positive pyogenic organisms in 88 of the 298 patients for whom cultures were made after therapy. Of the remainder, cultures yielded a Gram-negative bacillus of the Esch. coli-A. aerogenes group in 143, K. pneumoniae in 9, Ps. aeruginosa in 7, and P. vulgaris in 4. In addition, yeast organisms were present after penicillin therapy in eight instances. Friedman [63] has also reported a case in which Candida was recovered from the sputum after combined therapy with penicillin and streptomycin aerosol. Of 76 patients in this series treated with the broad-spectrum drugs and 5 patients recently treated, 46

TABLE 5.—*Summary of Effects of Aureomycin, Terramycin, and Chloramphenicol in Bronchiectasis and Chronic Bronchitis*

	Diagnosis	No. of Cases	Improvement		
			Marked	Moderate	Slight or None
Aureomycin	Bronchiectasis	11	5	4	2
Terramycin	Bronchiectasis	7	4	2	1
Chloramphenicol	Bronchiectasis	13	5	6	2
Aureomycin	Chronic bronchitis	13	5	5	3
Terramycin	Chronic bronchitis	10	3	7	..
Chloramphenicol	Chronic bronchitis	22	11	6	5
Total		76	33	30	13

exhibited no Gram-positive organisms on culture after treatment. Of the remainder, cultures of 11 yielded M. pyogenes var. aureus; of 11, P. vulgaris; of 7, K. pneumoniae, and of 1 each, Ps. aeruginosa, A. aerogenes, and C. albicans. In three patients of this series, a hemolytic streptococcus was cultured after chloramphenicol therapy. This was accompanied by acute pharyngitis and laryngitis, which appeared to respond promptly to intramuscular injection of penicillin. In two additional patients not reported in this series acute pharyhgitis and laryngitis developed while

62. Barach, A. L.; Silberstein, F. H.; Oppenheimer, E. T.; Hunter, T., and Soroka, M.: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**:485, 1945. Barach, A. L., and Garthwaite, B.: Physiologic and Antibiotic Therapy of Intractable Bronchial Asthma, Ann. Allergy **5**:297, 1947. Barach, A. L.; Garthwaite, B., and Rule, C.: The Use of Penicillin Aerosol in Bronchopulmonary and Sinus Infections, New York J. Med. **46**:1703, 1946. Barach, A. L.; Garthwaite, B.; Rule, C.; Talbot, T. R.; Kernan, J. D.; Babcock, J., and Brown, G.: Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis, Am. J. Med. **1**:268, 1946. Garthwaite, B.; Barach, A. L.; Levenson, E., and Rader, D.: Penicillin Aerosol Therapy in Bronchiectasis, Lung Abscess and Chronic Bronchitis, ibid. **3**:261, 1947. Barach, A. L.; Garthwaite, B.; Levenson, E., and Rader, D.: Physiologic and Antibiotic (Penicillin) Therapy in Chronic Hypertrophic Pulmonary Emphysema, Dis. Chest **13**:91, 1947.

63. Friedman, L. L.: Aerosol Therapy of Bronchopulmonary Diseases, Dis. Chest **16**:848, 1949.

TABLE 6.—*Effect of Aureomycin, Terramycin and Chloramphenicol on Chronic Bronchitis in Patients with Bronchial Asthma (Cases 1 to 30) and Pulmonary Emphysema (Cases 31 to 45)*

Case No.	Sputum Smear and Culture: Before Treatment	Sputum Smear and Culture: After Treatment	Drug	Dose, Gm.	Comment
1	Moderate pus cells; Str. viridans	Few pus cells	Aureomycin	10	Moderate improvement in asthma and cough
2	Few pus cells; Str. viridans	Few pus cells	Aureomycin	6	Marked exacerbation of asthma
3	Few pus and eosinophiles; hemolytic streptococci; M. pyogenes aureus	Few pus cells	Aureomycin	12	Asthma improved; sputum became white
4	Moderate pus cells; K. pneumoniae; M. pyogenes aureus	Few eosinophiles; no pus cells; occasional K. pneumoniae	Aureomycin	8	Marked improvement in breathing; sputum scanty and white
5	Purulent sputum	Moderate pus cells	Aureomycin	10	No effect
6	Many pus cells; hemolytic streptococci; M. pyogenes aureus	Few pus cells; occasional M. pyogenes aureus	Aureomycin	6	Marked improvement in asthma; sputum decreased and white
7	Many pus cells; hemolytic streptococci	Mucoid; few Str. viridans	Aureomycin	10	Sputum diminished; cough improved
8	Few pus cells and eosinophiles; Pneumococcus and K. pneumoniae	No pus cells; sterile	Terramycin	9	Moderate improvement and disappearance of cough
9	Few pus cells; occasional eosinophiles; Pneumococcus and M. pyogenes aureus	Few pus cells; many eosinophiles; few M. pyogenes aureus	Terramycin	12	Moderate improvement in cough
10	Moderate pus cells and Pneumococcus	Few pus cells; P. vulgaris	Terramycin	10	Much better; asthma subsided; no cough
11	Moderate pus cells; M. pyogenes aureus and Pneumococcus	No pus cells; occasional K. pneumoniae	Terramycin	15	Moderate improvement
12	Moderate pus cells and Pneumococcus	No pus cells; P. vulgaris	Terramycin Terramycin	10 9	Lessened wheezing and sputum; cough disappeared
13	Moderate pus cells; Str. viridans	Few pus cells	Terramycin	11.5	Marked decrease in sputum and wheezing
14	Many pus cells; hemolytic streptococci	Mucoid; few colonies of Str. viridans	Terramycin	10	Sputum diminished; cough improved
15	Few pus cells; hemolytic Streptococcus; Pneumococcus	No pus cells; occasional M. pyogenes aureus	Chloramphenicol	8	Patient also had upper respiratory tract infection; marked improvement
16	Moderate pus cells; K. pneumoniae	No pus cells; sterile	Chloramphenicol	12	Patient also had sinusitis; nose cleared; asthma markedly improved
17	Few pus cells; Str. viridans	Few pus cells	Chloramphenicol	6	Slight improvement of asthma
18	Moderate pus cells; Str. viridans	No pus cells	Chloramphenicol	8	Patient also had upper respiratory tract infection; cough improved greatly
19	Few pus cells; Str. viridans predominant	No pus cells; occasional Str. viridans	Chloramphenicol	8	Sputum decreased and white; asthma better
20	Few pus cells; K. pneumoniae	.....	Chloramphenicol	8	Sputum became white but no improvement clinically
21	Many pus cells; Pneumococcus; K. pneumoniae	No pus cells; Gram-negative diplococci	Chloramphenicol	8	Asthma and cough better; sputum white
22	Few pus cells; M. pyogenes aureus; Str. viridans	Occasional pus cells; M. pyogenes aureus	Chloramphenicol	8	Sputum decreased in amount; cough diminished
23	Many pus cells; hemolytic Streptococcus; M. pyogenes aureus	Few pus cells; M. pyogenes aureus	Chloramphenicol	8	Marked improvement in asthma; sputum decreased, white
24	Moderate no. of pus cells and eosinophiles; Streptococcus; M. pyogenes aureus	No pus cells; occasional eosinophiles; occasional colony of M. pyogenes aureus	Chloramphenicol	10	Moderate improvement
25	Many pus cells and eosinophiles	Rare pus cell; N. catarrhalis	Chloramphenicol	10	Moderate improvement
26	Moderate pus cells; Pneumococcus; hemolytic Streptococcus	Occasional pus cells; Gram-negative bacilli (occasional K. pneumoniae)	Chloramphenicol	8	Much better; cough and sputum decreased
27	Moderate pus cells; Str. viridans; K. pneumoniae	No pus cells; few Str. viridans	Chloramphenicol	10	Patient also had upper respiratory tract infection; asthma; cough and fever cleared

TABLE 6.—*Effect of Aureomycin, Terramycin and Chloramphenicol on Chronic Bronchitis in Patients with Bronchial Asthma (Cases 1 to 30) and Pulmonary Emphysema (Cases 31 to 45)—Continued*

Case No.	Sputum Smear and Culture		Drug	Dose, Gm.	Comment
	Before Treatment	After Treatment			
28	Moderate pus cells; Str. viridans	No pus cells; few N. catarrhalis	Chloramphenicol	30	Slight improvement in asthma; no sputum but cough persisted
29	Moderate pus cells; Pneumococcus; Str. viridans	Occasional pus cells; N. catarrhalis	Chloramphenicol	9	Great improvement; cough and sputum diminished; patient also had sinusitis
30	Moderate pus cells; hemolytic Streptococcus	Occasional pus cells; hemolytic Streptococcus	Chloramphenicol	10	Moderate improvement; red pharynx; hemolytic Streptococcus infection treated with penicillin
31	Many pus cells; Pneumococcus	Few pus cells; Str. viridans	Aureomycin	10	Marked decrease in cough and dyspnea
32	Moderate pus cells; few eosinophiles; Pneumococcus; K. pneumoniae	No pus cells; occasional eosinophiles; few colonies of M. pyogenes aureus	Aureomycin	12	Cough gone; breathing better
33	Moderate pus and eosinophiles; M. pyogenes aureus	Few pus cells; occasional colony of M. pyogenes aureus	Aureomycin	8	No improvement in breathing but cough better
34	N. catarrhalis; H. influenza; Str. viridans predominant; moderate pus cells	N. catarrhalis; H. influenza; few pus cells	Aureomycin	15	Marked improvement in cough and sputum
35	Moderate pus cells; hemolytic Streptococcus; M. pyogenes aureus	No pus cells; sterile	Aureomycin	10	Sputum changed from green to white; dyspnea improved
36	Many pus cells; hemolytic Streptococcus	Mucoid; few Str. viridans	Aureomycin	10	Sputum diminished; cough improved
37	Moderate pus cells; M. pyogenes aureus; Pneumococcus	No pus cells; occasional K. pneumoniae	Terramycin	15	Moderate improvement
38	Moderate pus cells; A. aerogenes; K. pneumoniae	No pus cells; occasional eosinophiles; sterile	Terramycin	12	Asthma almost completely disappeared; sputum decreased and white
39	Many pus cells; hemolytic Streptococcus	Mucoid; few colonies of Str. viridans	Terramycin	10	Sputum diminished; cough improved
40	Moderate pus cells; Pneumococcus; K. pneumoniae	Few pus cells; M. pyogenes aureus and Pneumococcus	Chloramphenicol	9	Patient also had sinusitis; slight benefit
41	Many pus cells; M. pyogenes aureus; Pneumococcus	No pus cells; sterile	Chloramphenicol	8	Marked improvement; sputum became white; cough diminished
42	Few pus cells; Str. viridans predominant	No pus cells; occasional Str. viridans	Chloramphenicol	8	Sputum decreased and white; asthma better
43	Moderate pus cells; hemolytic Streptococcus	Few pus cells; P. vulgaris; hemolytic Streptococcus	Chloramphenicol	12	No significant benefit; laryngitis 5 days later, treated with penicillin
44	Moderate pus cells; Str. viridans	Few pus cells; P. vulgaris	Chloramphenicol	12	Moderate improvement; laryngitis 6 days later, treated with penicillin
45	Many pus cells; Str. viridans; K. pneumoniae	No pus or sputum	Chloramphenicol	14	Marked improvement

they were taking chloramphenicol. From cultures of one a hemolytic M. pyogenes var. aureus was recovered, whereas no growth was obtained from those of the other.

The development of bronchopulmonary infection with the highly resistant organisms mentioned above, following broad-spectrum antibiotic therapy, constituted an unforeseen and grave complication. In three cases of advanced bronchiectasis, multiple antibiotic therapy, including administration of the broad-spectrum drugs, was followed by P. vulgaris infection and death. In the third case cultures of sputum yielded P. vulgaris and Ps. aeruginosa before death, but cultures of material from the lung taken at autopsy revealed Gram-negative chromogenic rods and yeast organisms. The case is included under P. vulgaris infection, but the other resistant organisms may have contributed to the final infection. The fourth

fatality occurred in a case of bronchiectasis and cirrhosis of the liver treated with terramycin; a fungus, the Cryptococcus, was grown from the lungs and the peritoneal fluid obtained at autopsy, death being due to general peritonitis. The finding of a fungus on lung sections at autopsy in a patient who had leukemia and repeated attacks of lobular pneumonia was ascribed by the pathologist to aspergillosis. The sixth case of infection and death associated with highly resistant organisms was that of a patient with pulmonary fibrosis whose cough and purulent expectoration were partially controlled with chloramphenicol during the last six months of life. Ps. aeruginosa appeared to be responsible for the final infection, being present in sputum culture before death and in lung cultures obtained at autopsy. The development of a fatal septicemia due to P. vulgaris, with 14 positive blood cultures, took place after multiple antibiotic therapy and cystoscopy in a patient with pneumonitis who also manifested metastatic (?) involvement of a supraclavicular lymph node. This case, the seventh instance of fatality, may have represented the joint effect of broad-spectrum antibiotic therapy and instrumentation of the urinary tract.

Of three patients with bronchiectasis now under observation, P. vulgaris infection was apparently due to the simultaneous eradication of the ordinary Gram-positive and Gram-negative bacteria by the broad-spectrum drugs in two and by the combined use of penicillin, streptomycin, and sulfadiazine therapy in the third. The case histories of these 10 patients and of 3 with a favorable response to antibiotic therapy are cited at the end of the paper. The serious complications described above occurred in patients with debilitating and extensive diseases, in most cases after prolonged therapy.

When treatment with the broad-spectrum drugs was carried out for more than six or seven days, undesirable reactions were frequent. One of four patients treated with aureomycin or terramycin experienced anorexia and nausea. Of the chloramphenicol-treated group, one of seven experienced a bitter metallic taste in the mouth, although this sensation did not prevent further therapy. The majority of patients treated with the newer antibiotic drugs had loose, bulky stools, and at times diarrhea, between the third and the sixth day of treatment; in some of the earlier-treated patients this was associated with perianal irritation and vaginitis. In 12 patients whose stools were examined daily, a pronounced fall in the number of Gram-negative organisms occurred after the second to the fourth day of treatment, with a corresponding growth of yeast forms in each case. In one patient Candida was obtained by smear and culture from the vagina and from the buccal mucous membrane. Involvement of the oral mucous membrane, accompanied by vulval and anal irritation, was reported by Harris [64] in 25 of his 110 cases. In nine of his cases C. albicans was recovered on culture, while a Cryptococcus was isolated from the furred tongue in the 10th. In a review of the side effects of aureomycin,[65] annular stomatitis, cheilosis, and irritation of the skin about the anus have been reported in a number of cases. Hewitt and Williams [58] noted three instances of aphthous ulcerations of the buccal mucosa in a series of patients treated with

64. Harris, H. J.: Aureomycin and Chloramphenicol in Brucellosis, with Special Reference to Side Effects, J. A. M. A. **142**:161, 1950.

65. Side-Effects of Aureomycin, Brit. M. J. **1**:1184, 1950.

chloramphenicol. A recent paper by Woods, Manning, and Patterson [66] supports the data published by Harris; in 25 patients treated with penicillin, aureomycin, and chloramphenicol Candida was recovered on culture, with the infections falling into three general groups: (*a*) infection of the oropharynx and esophagus; (*b*) invasion of the intestinal tract, with diarrhea, and (*c*) pulmonary moniliasis. While the incidence of gastrointestinal irritation varied considerably in the series reported,[67] the experience of others, as well as our own, indicates that chloramphenicol can be administered in higher doses without provoking nausea or vomiting than can either aureomycin or terramycin. Moreover, in only a relatively small percentage of the cases reported was the gastrointestinal intolerance so severe as to make discontinuance of therapy necessary.

Although pruritus ani has been a frequent complaint, this complication has not occurred during the last 100 courses of therapy, presumably the result of our instructions to the patient to wash the anus with warm water thoroughly after each bowel movement and then dry the perianal region with a gentle application of toilet paper. The conventional rubbing of the skin after a bowel movement may be responsible for carrying Candida infection into the mucous membrane and skin. In cases in which diarrhea has developed the ingestion of 1 qt. (1,000 cc.) of acidophilus milk daily, or 6 oz. (180 cc.) of acidophilus culture,[68] appeared to eliminate or reduce the number of loose stools when treatment was terminated. Although the anus-washing maneuver seemed to prevent perianal infection with Candida, stool cultures continued to demonstrate that the intestine harbored the Candida organisms.

The antacid preparations with aluminum hydroxide which were used to alleviate the gastric irritation so common with aureomycin and terramycin were found by Seed and Wilson [69] to interfere with the absorption of aureomycin. However, this interference was not noted when "mucotin" (a preparation of mucin, aluminum hydroxide, and magnesium trisilicate) [70] was substituted for the aluminum gel preparations.[71]

Sensitivity reactions to the newer antibiotics have been relatively infrequent as compared with allergic manifestations following the use of the sulfonamides, penicillin, and streptomycin. In the present series of 81 patients, 2 receiving chloramphenicol exhibited a generalized maculopapular eruption with pruritus. There

66. Woods, J. W.; Manning, I. H., Jr., and Patterson, C. N.: Monilial Infections Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207, 1951.

67. (*a*) Timpanelli, Huebner, and McDermott.[52b] (*b*) Caldwell and others.[52i] (*c*) Hewitt and Williams.[58] (*d*) Harris.[64] (*e*) Woods, Manning, and Patterson.[66] (*f*) Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: The Pharmacology of Terramycin in Animals and Man with Reference to Its Clinical Trial, Ann. New York Acad. Sc. **53**:245, 1950. (*g*) Sayer, R. J.; Michel, J. C.; Moll, F. C., and Kirby, W. M. M.: Terramycin: Clinical, Pharmacologic and Bacteriologic Studies, Am. J. M. Sc. **221**:256, 1951. (*h*) Knight, V.: Clinical Evaluation of Aureomycin, Chloramphenicol, and Terramycin, New York J. Med. **50**:2173, 1950.

68. The Arlington Chemical Company provided a commercial preparation, "basida," which was used by these patients.

69. Seed, J. C., and Wilson, C. E.: The Effect of Aluminum Hydroxide on Serum Aureomycin Concentrations After Simultaneous Oral Administration, Bull. Johns Hopkins Hosp. **86**:415, 1950.

70. Manufactured by The Harrower Laboratory, Inc.

71. Williams, M. L., and Weekes, D. J.: Effect of Antacid Preparations on Serum Aureomycin Levels, Rev. Gastroenterol. **18**:128, 1951.

were no instances of drug fever or granulopenia. Finland, Collins, and Paine,[72] and Knight [67h] did not observe any cutaneous sensitivities in their aureomycin-treated patients. Long and associates,[73] in appraising the toxicity of these three antibiotics, noted that drug fever was rare with administration of aureomycin but commoner with use of terramycin and chloramphenicol. However, Peck and Feldman [74] described three patients with allergic skin eruptions due to aureomycin. Volini and his co-workers [75] observed hemopoietic changes in three patients receiving chloramphenicol in which a severe, reversible granulocytopenia of the circulating blood was accompanied by an arrest in maturation of both the erythroid and the granulocytic elements of the bone marrow.

COMMENT

Although the broad-spectrum antibiotics result in the dramatic disappearance of purulent sputum and the signs of infection in respiratory disease, their prolonged employment in the treatment of chronic pulmonary infections has been shown to be attended by the serious risk of the development of secondary invaders which are highly resistant to known therapy, namely, P. vulgaris, Ps. aeruginosa, and yeast organisms. The secondary infections following the employment of penicillin, commented on in Part I, are far less frequent and more amenable to treatment. Thus, in two cases of K. pneumoniae infection following penicillin treatment with streptomycin was effective. In seven other cases, in which K. pneumoniae was present on culture of sputum and apparently interfered with further improvement from penicillin, chloramphenicol was employed for five days, with disappearance of the organisms and conspicuous clinical benefit. In eight additional cases in which the clinical condition remained stationary the elimination of Gram-negative coliform bacteria by either aureomycin or terramycin, given over a five-day period, resulted in subsequent improvement. The presence of Gram-negative bacteria in sputum culture did not appear to interfere with diminution or clearing of the infection in the majority of our cases.

When streptomycin was added to penicillin as a therapeutic agent, Candida organisms were frequently found on culture, but no instance of actual invasion was observed. In only one patient was the subsequent addition of streptomycin and sulfadiazine to a program of penicillin treatment followed by persistent infection with P. vulgaris, as reviewed in the case histories that follow. Of the other 298 patients treated with penicillin, Ps. aeruginosa was recovered in cultures of the sputum in 7 and P. vulgaris was isolated in only 4, with true invasion in the patient referred to above, in whom the Gram-negative flora were reduced by addition of prolonged streptomycin and sulfonamide therapy.

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72. Finland, M.; Collins, H. S., and Paine, T. F.: Aureomycin: A New Antibiotic, Results of Laboratory Studies and of Clinical Use in 100 Cases of Bacterial Infections, J. A. M. A. **138**:946, 1948.

73. Long, P. H.; Bliss, E. A.; Schoenbach, E. B.; Chandler, C. A., and Bryer, M. S.: The Experimental Background and Clinical Use of Antibiotics, Lancet **1**:1139, 1951.

74. Peck, S. M., and Feldman, F. F.: Sensitivity Reactions to Aureomycin, J. A. M. A. **142**:1137, 1950.

75. Volini, I. F.; Greenspan, I.; Ehrlich, L.; Gonner, J. A.; Felsenfeld, O., and Schwartz, S. O.: Hemopoietic Changes During Administration of Chloramphenicol (Chloromycetin), J. A. M. A. **142**:1333, 1950.

In contrast to these results, of 81 patients who received aureomycin, terramycin, and chloramphenicol, P. vulgaris was recovered from the sputum culture in 11 and active infection took place in 6. The death of seven patients was associated with the presence of highly resistant organisms, and of four with P. vulgaris. One death was due to Ps. aeruginosa; one, to Cryptococcus peritonitis, and one in part to lobar pneumonia due to aspergillosis, the yeast organisms being found on microscopic section of the lungs. These complications occurred in patients with debilitating diseases, generally after prolonged treatment.

Bloomfield [76] has recently emphasized the disturbance in balance of the normal bacterial flora of the upper respiratory tract and the gastrointestinal system that follows antibiotic therapy. During treatment with the broad-spectrum drugs, secondary invaders, predominantly P. vulgaris, Ps. aeruginosa, and Candida, have been observed by a number of investigators in cultures of the urine, sputum, blood, mucous membranes, and skin.[77] Finland [78] has encountered in several patients treated with aureomycin and terramycin a severe diarrhea, apparently resulting from enteritis due to a hemolytic M. pyogenes var. aureus; in addition, scarlet fever was observed in four patients who had received terramycin, with the pharyngeal cultures revealing hemolytic M. pyogenes var. aureus and no hemolytic streptococci. In the 12 of the 200 patients treated with chloramphenicol who had glossitis, stomatitis, and pharyngitis, Williams [79] concluded that the condition was apparently caused by C. albicans.

The problem of resistance of certain strains of organisms to penicillin and streptomycin and the development of a "step-wise" increase in resistance during the period of administration of antibiotics, especially streptomycin, has received much attention.[80] Finland,[78] who stressed the increasing frequency of resistant strains of hemolytic M. pyogenes var. aureus recovered from the respiratory tract and other sources, found that a large proportion of the strains of this organism were resistant to aureomycin and terramycin. Spink [80e] found that 45 of 104 strains of M. pyogenes var. aureus were highly resistant to penicillin. Only one strain was resistant to aureomycin and five to terramycin; on a weight-for-weight basis all the strains were more resistant to chloramphenicol than to either of the other two antibiotics. In the studies carried out on Gram-negative organisms by

76. Bloomfield, A. L.: Effect of Antibiotics on Bacteria of the Upper Air Passages, A. M. A. Arch. Int. Med. **88**:135, 1951.

77. (*a*) Caldwell and others.[52i] (*b*) Finland and others.[59] (*c*) Knight.[67b] (*d*) Harvey, J. C.; Mirick, G. S., and Schaub, I. G.: Clinical Experience with Aureomycin, J. Clin. Invest. **28**:987, 1949. (*e*) Yow, E. M.: Infections Due to Pseudomonas Aeruginosa Developing During Antibiotic Therapy, Am. J. Med. **11**:254, 1951.

78. Finland, M.: The Present Status of Antibiotics in Bacterial Infections, Bull. New York Acad. Med. **27**:199, 1951.

79. Williams, B., Jr.: Oral and Pharyngeal Complications of Chloramphenicol (Chloromycetin) Therapy, Am. Pract. & Digest Treat. **1**:897, 1950.

80. (*a*) Long and others.[73] (*b*) Yow.[77e] (*c*) Sherris, J. C., and Florey, M. E.: Relation of Penicillin Sensitivity in Staphylococci to Clinical Manifestations of Infection, Lancet **1**:309, 1951. (*d*) Rountree, P. M.; Barbour, R. G. H., and Thomson, E. F.: Incidence of Penicillin-Resistant and Streptomycin-Resistant Staphylococci in a Hospital, Lancet **1**:435, 1951. (*e*) Spink, W. W.: Clinical and Biological Significance of Penicillin-Resistant Staphylococci, Including Observations with Streptomycin, Aureomycin, Chloramphenicol, and Terramycin, J. Lab. & Clin. Med. **37**:278, 1951.

Hewitt and Williams,[58] the majority of the strains of Ps. aeruginosa and about half the strains of P. vulgaris proved to be resistant to chloramphenicol. Apparently, as a result of high resistance, these organisms, as well as chromogenic Gram-negative rods, became the predominant type recovered after antibiotic treatment of urinary infections.[81]

Most of the strains of the B. coli group and K. pneumoniae found in sputum cultures of patients with chronic bronchitis treated with penicillin aerosol were found to be clinically sensitive to streptomycin or the broad-spectrum antibiotics. However, the treatment of resistant organisms, appearing after administration of broad-spectrum antibiotics, such as P. vulgaris, Ps. aeruginosa, and Candida, is obviously more difficult. Perhaps some of the newer antibiotics, such as polymyxin B, which is active against Ps. aeruginosa [82]; fungicidin,[83] which appears to inhibit C. albicans and Cryptococcus, may be helpful, but neomycin, which may be effective against P. vulgaris, is too toxic for safe clinical use. The use of diethyldiaminoethyl iodide penicillin was found clinically effective in three cases of P. vulgaris infection; the amount of purulent expectoration was sharply reduced, but the organism persisted on culture.

Speck, Jawetz, and Gunnison [84] reported that all three of the broad-spectrum antibiotics are capable of interfering with the action of penicillin, both in vitro and in experimental infections in mice. Except for the synergism displayed by combinations of penicillin and streptomycin, the additive effect of two or more of the other antibiotics given simultaneously is questionable. Studies by Herrill, Heilman, and Wellman [54] on Gram-negative organisms made resistant to the broad-spectrum antibiotics showed a retention of their sensitivity to streptomycin, suggesting the possible importance of subsequent administration of streptomycin after the use of aureomycin, terramycin, or chloramphenicol.

In the present series it was noted that patients with extensive bronchiectasis generally suffered a recurrence of their infection, evidenced by return of cough and purulent sputum, within two to four weeks after a course of the broad-spectrum antibiotics, except when their administration was initiated for the treatment of an exacerbation due to acute respiratory illness. In the latter circumstance, favorable clinical effects persisted as a result of eradication of the superimposed infection. Similarly, in patients with bronchial asthma and pulmonary emphysema, in whom increased bronchospasm frequently took place after an acute infection of the upper respiratory tract, it seemed possible to arrest the disease and, in some cases, to prevent the usual worsening of asthmatic dyspnea by antibiotic therapy. Furthermore, these newer antimicrobial agents were administered repeatedly for brief courses, with only rare manifestations of an allergic nature, perhaps their chief

81. Wheat, R. P.; Zuckerman, A., and Rantz, L. A.: Infection Due to Chromobacteria: Report of 11 Cases, A. M. A. Arch. Int. Med. **88**:461, 1951. Waisbren, B. A.: Bacteremia Due to Gram-Negative Bacilli Other Than the Salmonella: A Clinical and Therapeutic Study, ibid. **88**:467, 1951.

82. Hayes, E. R., and Yow, E.: Meningitis Due to Pseudomonas Aeruginosa Treated with Polymyxin B, Am. J. M. Sc. **220**:633, 1950.

83. Hazen, E. L., and Brown, R.: Fungicidin, an Antibiotic Produced by a Soil Actinomycete, Proc. Soc. Exper. Biol. & Med. **76**:93, 1951.

84. Speck, R. S.; Jawetz, E., and Gunnison, J. B.: Studies on Antibiotic Synergism and Antagonism, A. M. A. Arch. Int. Med. **88**:168, 1951.

advantage over penicillin for treatment of the pyogenic infections of the respiratory tract in the cases under discussion.

Since Gram-positive bacteria are responsible for the vast majority of cases of chronic infection, administration of penicillin is considered the mainstay of therapy, with the use of the broad-spectrum antibiotics to eradicate Gram-negative bacteria when penicillinase production apparently hampers further progress or in the event that a superinfection with an organism, such as K. pneumoniae, takes place. According to Chandler and associates,[85] aureomycin eliminates the penicillinase-producing quality of resistant organisms of M. pyogenes var. aureus type, rendering them thereby again sensitive to penicillin.

The clinical effectiveness of these agents is related not only to their widespread bacterial inhibition but also to the fact that they are excreted in the sputum in small amounts. This ready diffusibility across the bronchial barrier is quite in contrast to that of penicillin sodium, which, except in cases of lobar pneumonia, is not found in the expectoration after parenteral administration. Until recently, the only method whereby effective sputum concentration of penicillin could be attained consisted in the inhalation of penicillin aerosol or dust. However, Jensen and associates [86] have now developed an ester of penicillin, benzyl penicillin diethylaminoethyl ester hydriodide, which is concentrated in the lungs and appears in the sputum after intramuscular injection. These findings have been confirmed by Heathcote and Nassau,[87] who presented the favorable results of the clinical use of this ester in patients with bronchopulmonary infection. The results of preliminary studies on 40 patients treated in our clinic have been encouraging, and will be reported in full later [88]; it may be said at this time, however, that prompt decrease in the purulent quality of the sputum took place in the majority of patients treated, with the presence concomitantly of effective concentrations of penicillin in the sputum, from 0.1 to 0.8 unit per milliliter. The employment of the diethylaminoethyl ester of penicillin by intramuscular injection is now being tested on a large series of patients as the penicillin product of choice with the use of the broad-spectrum antibiotics, as intimated above, for brief periods to counteract either actual invasion with Gram-negative bacteria or penicillinase production in the event of the failure of adequate benefit from penicillin alone.

Drainage in chronic bronchopulmonary infections, admittedly impaired in most cases, may in part account for the serious nature of the complications with resistant

85. Chandler, C. A.; Davidson, V. Z.; Long, P. H., and Monnier, J. J.: Studies on Resistance of Staphylococci to Penicillin: Production of Penicillinase and Its Inhibition by the Action of Aureomycin, Bull. Johns Hopkins Hosp. **89**:81, 1951.

86. Jensen, K. A.; Dragsted, P. J.; Møller, P., and Kiær, I.: Investigation of Penicillin Preparations and Dosage Schedules I, Ugesk. læger **112**:1043, 1950. Jensen, K. A.; Dragsted, P. J., and Kiær, I.: Studies on the Therapeutic Effect of Leocillin, ibid. **113**:1039, 1951; Leocillin (Benzyl Penicillin-β-Diethylaminoethylester Hydriodide), Acta path. et microbiol. Scandinav. **28**:407, 1951.

87. Heathcote, A. G. S., and Nassau, E.: Concentration of Penicillin in the Lungs: Effects of Two Penicillin Esters in Chronic Pulmonary Infections, Lancet **1**:1255, 1951.

88. Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Advances in the Treatment of Non-Tuberculous Pulmonary Disease, Bull. New York Acad. Med. **28**:353, 1952. Barach, A. L.; Rose, H.; Bickerman, H. A., and Melcher, G. W., Jr.: Clinical and Pharmacological Studies with Diethyl Aminoethyl Penicillin, to be published.

organisms in this series, which are reported, in the attempt to outline the limitations, as well as the advantages, of the use of the broad-spectrum antibiotics. Interference with drainage in urinary infections may also be responsible in part for the new infections with resistant organisms which have recently been reported to follow terramycin therapy.[89]

The recent study of Pappenfort and Schnall [90] not only revealed the consistent presence of yeast organisms in each of 16 cases in which inflammatory disease appeared in the mouth, vagina, and perianal region after the use of aureomycin, but also indicated that this drug stimulated the growth of C. albicans and Cryptococcus neoformans in vitro. This evidence is presented in support of the program formulated above for the treatment of chronic infections of the respiratory tract.

SUMMARY

The results of a long-term and a recent study of antibiotic therapy of chronic infections of the respiratory tract are presented. The diseases which have received special emphasis are chronic bronchitis and bronchiectasis, frequently in association with such related clinical entities as bronchial asthma, pulmonary emphysema, and pulmonary fibrosis.

The antibiotics studied included penicillin, administered chiefly by inhalation, and the broad-spectrum antibiotics, aureomycin, terramycin, and chloramphenicol. A preliminary report of the use of the diethylaminoethyl ester of penicillin is presented.

The principles and methods of administration of antibiotic aerosols, especially penicillin, are described. The clinical results of penicillin treatment, in the main by nebulization, are summarized as follows: Significant improvement, i. e., pronounced or moderate, took place in 58 of 70 cases of bronchiectasis, 46 of 50 cases of chronic bronchitis without clinical evidence of bronchospasm, and 97 of 200 cases of chronic bronchitis occurring in association with bronchial asthma or the bronchospastic type of pulmonary emphysema. The presence of bronchospasm interfered with complete relief of the symptoms of cough and expectoration in cases in which allergic, as well as infectious, factors played an etiological role. Significant improvement as a result of aerosol therapy, employed in conjunction with intermittent negative pressure applied to the accessory sinus cavities, took place in 36 of 40 cases of acute sinusitis and in 103 of 150 cases of chronic sinusitis.

The clinical improvement following 50 courses of penicillin dust administered to patients with chronic bronchitis and bronchiectasis was similar to that achieved with aerosol therapy. However, penicillin blood levels after inhalation of penicillin dust were sharply lower than those recorded after comparable doses of aerosol penicillin. Furthermore, the local side-effects and the tendency to produce severe bronchospasm were enhanced by administration of penicillin in powder form. In the routine treatment of bronchial asthma and the bronchospastic type of pulmonary

89. Womack, C. R.; Jackson, G. G.; Gocke, T. M.; Kass, E. H.; Haight, T. H., and Finland, M.: Terramycin Therapy of Urinary Tract Infections, A. M. A. Arch. Int. Med. **89**:240, 1952.

90. Pappenfort, R. B., and Schnall, E. S.: Moniliasis in Patients Treated with Aureomycin: Clinical and Laboratory Evidence That Aureomycin Stimulates the Growth of Candida Albicans, A. M. A. Arch. Int. Med. **88**:729, 1951.

emphysema administration of penicillin by the systemic route is recommended. The chief indications for aerosol penicillin therapy are considered to be bronchiectasis, sinusitis, lung abscess, and pneumonitis due to organisms which have acquired unusual resistance, such as M. pyogenes var. aureus.

Sputum cultures after effective penicillin treatment of infections by Gram-positive bacteria consistently show Gram-negative bacteria, especially coliform organisms, K. pneumoniae, or A. aerogenes. Of a combined series of cases of infections of the respiratory tract treated with penicillin, P. vulgaris was found in only 4 of 298 cultures after treatment, with evidence of clinical invasion in none. In 17 cases the use of streptomycin or the broad-spectrum antibiotics was employed to counteract either infection with K. pneumoniae or to accomplish improvement apparently hampered by penicillinase production of Gram-negative bacteria or penicillinase production of resistant staphylococci.

In a single case of bronchiectasis in which prolonged treatment with streptomycin and sulfadiazine added to the use of penicillin, P. vulgaris was subsequently found as a persistent invader and the cause of chronic bronchial infection.

The results of treatment of chronic bronchopulmonary infections with aureomycin, terramycin, and chloramphenicol are summarized as follows: Significant benefit took place in 37 of 45 cases of chronic bronchitis, associated with bronchial asthma or pulmonary emphysema, and in 26 of 31 cases of bronchiectasis. The clinical improvement is correlated with corresponding evidence of elimination or reduction of pus in the sputum and eradication or reduction of pyogenic organisms on sputum cultures.

Prolonged arrest of infection in cases of chronic bronchitis and bronchiectasis, generally in association with bronchial asthma or pulmonary emphysema, has been initiated both by penicillin and by the broad-spectrum antibiotics, with, at times, a remarkable restoration of health, relief of dyspnea, and disappearance of productive cough. The clinical results in this study indicate that penicillin is desirable as the mainstay of treatment when the aim of treatment is a long-maintained arrest of chronic infection. The basis for this opinion is that (1) in most instances the infection is initially due to Gram-positive bacteria; (2) occasional infections by Gram-negative flora may be generally controlled by short courses of the broad-spectrum antibiotics or streptomycin; (3) the penicillinase production of Gram-negative bacteria or resistant M. pyogenes var. aureus is usually eliminated by the temporary use of the newer antibiotics; (4) the hazard of development of highly resistant organisms, such as P. vulgaris, Ps. aeruginosa, and yeast organisms, as a result of prolonged elimination of the ordinary Gram-negative and Gram-positive bacteria. The broad-spectrum antibiotics are, however, of unique value when administered for limited periods, following penicillin therapy, in the circumstances listed above.

Although the relatively normal person does not generally require antibiotic therapy for infections of the upper respiratory tract, patients with chronic bronchitis and bronchiectasis, frequently in association with bronchial asthma and pulmonary emphysema, may suffer extension of pulmonary disease and increased bronchospasm as a result of an acute exacerbation of the chronic disease process. Broad-spectrum antibiotic therapy for a period of five to six days has the advantage, in most cases, of prompt control of infection, with a minimum of allergic response.

The risk of allergic reactions to prolonged penicillin treatment seems less hazardous than the danger of infection with new highly resistant bacteria which may occur after prolonged therapy with the broad-spectrum drugs. Of 81 cases in which the broad-spectrum antibiotics were used, a fatal outcome was associated with the presence of infection by these highly resistant organisms in 7. However, in each case a debilitating advanced chronic disease had previously been present, and other contributing factors were frequently present; thus, in one patient cystoscopy appeared to be a precipitating influence, since P. vulgaris septicemia followed this diagnostic procedure. Nevertheless, the emergence of resistant strains is significant; in two additional cases of bronchiectasis a chronic P. vulgaris infection is now present, the apparent consequence of too long-continued use of the broad-spectrum antibiotic drugs. The prolonged simultaneous eradication of the common Gram-positive and Gram-negative flora in serious advanced suppurative disease of the lungs should, therefore, be undertaken with caution, and broad-spectrum antibiotic therapy should be terminated when P. vulgaris or other highly resistant organisms appear in cultures of sputum.

The use of the diethylaminoethyl ester of penicillin is based on its presence in lung tissue in concentrations 5 to 10 times that of procaine penicillin G after intramuscular injection. Effective levels of the drug are also secreted into the sputum. The early results in a series of 40 patients with bronchiectasis and chronic bronchitis, occurring in the main in patients with pulmonary emphysema and bronchial asthma, indicate that the use of this compound is generally followed by an especially favorable response in infections due to Gram-positive bacteria.

The case histories of 13 patients are presented to illustrate the favorable clinical response to, as well as the complications which result from, antibiotic therapy of chronic bronchopulmonary disease.

Addendum: Illustrative Case Histories

Case 1.—In a woman aged 26, after an infection of the upper respiratory tract three years prior to admission, a chronic cough productive of scant mucoid, and occasionally yellow mucopurulent, sputum developed. Previous treatment had consisted of repeated antral irrigations. On her admission to the hospital, fine sibilant rales were heard over scattered areas on the posterior chest wall. The sputum revealed a few pus cells and had a predominantly mucoid appearance. Micrococcus pyogenes var. albus was found on culture. Roentgenograms of the sinuses revealed thickening of the left frontal, maxillary and ethmoid sinuses. Treatment consisted in the administration of penicillin for the first six days, as follows: 100,000 units inhaled five times a day through the mouth by mask; 100,000 units injected intramuscularly at four-hour intervals five times a day, and 50,000 units inhaled through the nose with the negative-pressure, aerosol-penicillin apparatus, four times daily. At the end of six days the treatment was continued solely with nasal inhalation of 50,000 units of penicillin, with intermittent negative pressure, four times daily for two more weeks. The sputum culture at the end of treatment revealed A. aerogenes. Rapid subsidence of symptoms took place, and the patient was discharged greatly improved. Cough and expectoration entirely disappeared two weeks later; there had been no recurrence during the four years prior to this report.

Comment.—A patient with chronic cough of three years' duration experienced complete relief of symptoms after four weeks' treatment, in the main with aerosol penicillin. Absence of any recurrence of symptoms for five years justifies the impression that the therapy resulted in a cure of both chronic bronchitis and chronic (ethmoid) sinusitis.

CASE 2.—A woman aged 54, after an episode of pneumonia seven years before, complained of progressive weakness, dyspnea, cough, mucopurulent sputum, expectoration, and bouts of fever. For three years the patient inhaled nebulized vaponefrin® for relief of wheezing and dyspnea and intermittently inhaled 50% oxygen with a meter mask. On admission, the patient appeared thin, tired, and dyspneic and had a cough productive of copious amounts of purulent sputum. The chest was emphysematous; breath sounds were prolonged; sibilant rales were heard throughout both lungs. Breathing was of the costal type, with movement of the accessory muscles of the neck. Roentgenograms of the lungs revealed bullae in the right upper lung field, accentuation of the bronchovascular markings, and a low, flat diaphragm. The sputum contained many pus cells, and on culture a Streptococcus of the viridans type and H. influenzae organisms were found. Aureomycin was administered, 2 gm. daily in four divided doses for 14 days. Acidophilus milk, 1 qt. (1,000 cc.) daily, was ingested throughout the course of treatment. The sputum was gradually reduced in amount and at the end of 10 days was free from pus cells, the culture revealing Neisseria catarrhalis. No side-effects, such as nausea or loose, frequent stools, were encountered. The patient's lungs were clear, and during the fourth week of her stay in the hospital cough and expectoration were virtually absent. Vaponefrin® and oxygen administration were discontinued. Diaphragmatic breathing was taught the patient. One year later she received a six-day course of terramycin for an acute febrile infection of the respiratory tract, with disappearance of cough and purulent expectoration. A marked improvement in general well-being was accompanied by a 30 lb. (13.6 kg.) gain in weight. The patient works in a garden and carries out ambulatory activity, without dyspnea or cough.

Comment.—The conspicuous relief of dyspnea, disappearance of bronchospasm, and gain in weight (30 lb.) were plainly due to complete clinical arrest of suppurative bronchitis associated with pulmonary emphysema. Prolonged treatment with aureomycin and a subsequent short course of terramycin therapy were not attended by adverse side-effects.

CASE 3.—A man, aged 26, reported that since the age of 8 months he had had chronic cough with purulent, frequently foul-smelling green sputum. Three attacks of pneumonia took place during childhood, and both the cough and the sputum increased. Administration of the sulfonamides, repeated courses of penicillin by intramuscular injection, and frequent bronchoscopic aspirations made little change in the patient's condition. Dyspnea on slight effort became increasingly worse. Bronchograms demonstrated severe cylindrical and saccular bronchitis in both lungs with a persistent peribronchial pneumonitis, evident on numerous hospitalizations prior to June, 1945. At this time penicillin aerosol therapy was instituted at home, 600,000 units daily for two weeks, followed by 200,000 units daily, divided into four inhalations. Improvement was not manifest for four weeks, but at the end of six weeks definite decrease in cough and expectoration was evident. At the end of four months' treatment the dyspnea on exertion was notably decreased; the patient had gained 35 lb. (11.9 kg.) and produced 1 to 2 oz. (30 to 60 cc.) of mucopurulent material daily, in contrast to the original average amount of 6 oz. (180 cc.) of purulent sputum daily. Cultures of the sputum prior to treatment revealed streptococci of the viridans group, H. influenzae and Hemophilus hemolyticus. During the past six years the patient has continued to use inhalations of aerosol penicillin in a dose which has varied from 50,000 to 100,000 units twice a day. Cultures of the sputum reveal the continued presence of Esch. coli, and at times A. aerogenes. Brief courses of the sulfonamides and streptomycin produce little alteration in expectoration. In March, 1951, cultures showed Esch. coli and H. influenzae. At this time he was given chloramphenicol, 1 gm. by mouth and 1 gm. intravenously, daily for five days. A distinct decrease in the purulent quality of the sputum took place. The patient was then continued on treatment with aerosol penicillin; he is at work and feels well.

Comment.—The inhalation of aerosol penicillin for six years in this case had the result of initiating a remarkable improvement, with the disappearance of cyanosis and dyspnea on moderate exertion, a striking reduction in purulent

expectoration, clearing of chronic peribronchial pneumonitis, and maintenance of reasonably good health, instead of a state of invalidism, from which he suffered prior to treatment. No increase in resistance of strains of Gram-positive bacteria was noted. Furthermore, the presence of Gram-negative micro-organisms has not interfered with the good results obtained, although their elimination for a brief period with chloramphenicol was followed by an even sharper reduction in the amount of purulent expectoration.

Case 4.—A man aged 50, after four episodes of pneumonia in a 10-year period preceding his first hospital admission, in 1947, presented dyspnea on exertion and a severe cough productive of 6 oz. (180 cc.) daily of foul, purulent sputum, with symptoms increasing during the preceding three years. Bilateral extensive bronchiectasis was revealed in the bronchogram. Postural drainage and sulfadiazine had not produced appreciable benefit. Culture of sputum on admission yielded coagulase-positive hemolytic M. pyogenes var. aureus, Streptococcus of the viridans type, and A. aerogenes. The treatment consisted of administration of penicillin, intramuscularly and by aerosol inhalation, which was followed by striking improvement, the sputum culture on discharge showing Streptococcus of the viridans group and a few colonies of H. influenzae. From 1947 to the end of 1949, intermittent courses of penicillin aerosol were given, with moderate improvement in cough and expectoration. At that time the sputum became foul, with the culture revealing a predominance of Esch. coli. For three months 0.3 gm. of streptomycin was added to the 300,000 units of penicillin by inhalation, and for the last three weeks sulfadiazine was given by mouth. In the beginning of 1950 P. vulgaris was revealed as the predominant organism. Aureomycin, 10 gm. in a five-day period, was administered, without change in the character of the sputum. Chloramphenicol was given in two courses of 2 to 3 gm. daily for a period of two weeks and for a period of four weeks. On each occasion the cough was much improved, and the expectoration was reduced to 1 oz. (30 cc.) daily, with, however, a foul odor and growths of P. vulgaris and Esch. coli on culture.

A course of diethylaminoethyl ester of penicillin, 2,000,000 units in two divided doses, given over a period of 12 days, resulted in virtual disappearance of cough and expectoration for six weeks, with a gradual increase in cough and sputum during the following two weeks. A second, similar course of diethylaminoethyl ester of penicillin for seven days resulted in a reduction of sputum from 16 to 2 oz. (480 to 60 cc.) daily, with disappearance of the foul odor. The sensitivity tests had previously shown that in vitro the P. vulgaris strain was not sensitive to penicillin.

Comment.—This case, the only one in this series in which chronic P. vulgaris infection developed as a result of treatment with a combination of penicillin with sulfadiazine and streptomycin, suggests that eradication of most Gram-negative and Gram-positive organisms may be produced by combined drug therapy, as well as by the broad-spectrum antibiotics. For the past two years the patient has received intermittent antibiotic therapy as outlined, together with procedures that produce mechanical drainage of the respiratory tract.

Case 5.—In a woman aged 57, a chronic cough productive of large amounts of purulent sputum followed an attack of pneumonia involving the right lower lobe in 1948. Six years previously she had a left nephrectomy for stag-horn calculi. The area of consolidation in the right lower lobe persisted despite adequate penicillin therapy. Repeated febrile episodes took place throughout 1948; cultures of the sputum yielded hemolytic streptococci. The clinical course suggested the diagnosis of bronchiectasis, and in 1949 she was started on a regimen of penicillin aerosol, 300,000 units being given daily for three weeks and then a maintenance dose of 200,000 units daily for two months. This was accompanied by a marked general improvement, with reduction in cough and sputum, and a gain in weight of 7 lb. (3.2 kg.). The sputum, however, continued to show the presence of pus, and a culture revealed K. pneumoniae. Combined streptomycin, 0.1 gm. and penicillin dust inhalations, 100,000 units, were given three times daily for six weeks, with notable benefit, which was to a large extent

maintained for almost one year, at which time K. pneumoniae organisms reappeared on culture of sputum and expectoration increased to 3 oz. (90 cc.) daily. On one occasion, inhalation of antibiotic dust precipitated severe bronchospasm and had to be discontinued. In June, 1950, she was given 1.5 gm. of aureomycin daily for three days; this regimen was discontinued because of nausea and vomiting. The substitution of chloramphenicol, 2 gm. daily for four days, resulted in a moderate reduction in sputum, but the K. pneumoniae persisted. No medication was given for a period of six months, during which time her cough and expectoration gradually increased. After administration of 1.5 gm. of terramycin, discontinued because of vomiting, and sulfisoxazole (gantrisin®), 2.0 gm. daily for five days, the sputum was reduced from 3 to 1 oz. (90 to 30 cc.), but culture then revealed P. vulgaris. During the subsequent two months expectoration again increased, with P. vulgaris found in four cultures. Culture of the urine at that time also revealed P. vulgaris. The patient was hospitalized and treated with 1 gm. of streptomycin for two days, but therapy was discontinued because of severe vestibular toxicity. The blood level of streptomycin remained very high for eight days, owing to impaired renal excretion. Sputum culture then revealed M. pyogenes var. aureus and Esch. coli. One month later an increase of purulent sputum to 3 oz. occurred. Diethylaminoethyl iodide penicillin, 1,000,000 units twice daily, was administered for 10 days, with marked improvement in general well-being. The sputum was white and mucoid, and the amount 1 oz. daily, at the end of treatment.

Comment.—The disappearance of P. vulgaris in this case appeared to follow the maintained high blood concentrations of streptomycin.

CASE 6.—A man aged 59, had a 30-year history of asthmatic wheezing and chronic cough, productive, during one year, of 10 to 12 oz. (300 to 360 cc.) of purulent sputum daily. Allergic management, use of bronchodilators, including vaponefrin,® and a course of hyposensitization to inhalant allergens afforded only slight and temporary relief. When he was first observed, he was in severe respiratory distress and intensely cyanotic. The sputum was thick and greenish and on culture yielded a hemolytic Streptococcus and hemolytic M. pyogenes var. aureus. The chest film revealed an area of pneumonic infiltration, with central rarefaction in the lower half of the left lung field, suggestive of a lung abscess. Inhalation of penicillin aerosol resulted in an acute exacerbation of bronchospasm.

Chloramphenicol was then administered, 2.5 gm. daily, for one week, with striking clinical improvement. The cough and sputum diminished but returned to the pretreatment level when the chloramphenicol dose was reduced. Accordingly, the patient was maintained on chloramphenicol for five months, receiving a total dose of 300 gm. Chest films repeated three weeks after onset of antibiotic therapy showed disappearance of the infiltration previously observed and apparent replacement of the abscess by a fibrotic scar. The patient was symptom-free except for slight dyspnea on moderate exertion. At the onset of the sixth month of continuous chloramphenicol therapy increase in cough was noted, productive of a foul-smelling purulent sputum. Cultures revealed the presence of P. vulgaris. Chloramphenicol therapy was stopped and combined penicillin and streptomycin were given parenterally for one month, with decrease in sputum and cough. Subsequent cultures revealed a few colonies of M. pyogenes var. albus and N. catarrhalis. During a recurrence of cough, with considerable increase in purulent sputum, the patient self-administered 1.5 gm. of chloramphenicol daily over a period of two weeks, without noticeable reduction in expectoration. Repeated cultures of the sputum revealed P. vulgaris. The patient was hospitalized because of increasingly severe dyspnea. Diethylaminoethyl iodide penicillin was given in a dose of 1,000,000 units twice daily for eight days.

The sputum, purulent before treatment and amounting to 2 oz. (60 cc.) daily, became mucoid and less than 1 oz. in amount. Culture continued to reveal P. vulgaris.

Comment.—Prolonged treatment with chloramphenicol preceded the development of P. vulgaris infection. Intermittent therapy with diethylaminoethyl iodide penicillin is now employed to ameliorate periods of recurrent cough and purulent expectoration.

CASE 7.—A youth aged 18 had been followed at the Presbyterian Hospital since the age of 4 years, when fibrocystic disease of the pancreas was first diagnosed. After an attack of

pneumonia at 7 years of age, a chronic cough productive of 2 to 3 oz. of purulent sputum developed. A second bout of pneumonia, in 1944, was treated with penicillin. Clubbing of the extremities was noted at this time. In 1946 a bronchogram revealed diffuse dilatation of the secondary bronchi of the left lower lobe, confirming the clinical diagnosis of bronchiectasis. Sputum culture showed the presence of a viridans type of streptococcus and H. influenzae.

He was treated over a period of three years with intermittent courses of sulfonamides by mouth, and penicillin and penicillin-streptomycin aerosol inhalations, with temporary symptomatic improvement. During this period the predominant organisms on sputum culture were H. influenzae and Esch. coli. In 1949, while he was receiving penicillin and streptomycin inhalations, K. pneumoniae was cultured for the first time. During 1950 he was given short courses of aureomycin and chloramphenicol, with moderate temporary improvement in cough and a decrease in sputum from 6 or 7 oz. (180 or 210 cc.) to 1 or 2 oz. (30 or 60 cc.) daily during treatment. After prolonged terramycin treatment, partly in the hospital and partly in the clinic, with a dosage of 1.5 gm. of terramycin daily for 60 days, P. vulgaris in pure culture was recovered from the sputum. During the last three weeks of treatment, the cough increased, and he became febrile and lost weight. Dyspnea became severe, necessitating hospitalization. Sputum cultures continued to show P. vulgaris. Marked respiratory acidosis was present, the pH of venous blood being 7.23 and the CO_2 content 45 mEq. Treatment with intravenous injection of chloramphenicol and oxygen was unsuccessful and he died on the fourth day of hospitalization.

At necropsy the left lower lobe was observed to be completely consolidated. Diffuse fibrosis was present throughout both lungs, and all the bronchi appeared dilated and contained a purulent exudate, from which P. vulgaris was cultured. The pancreas was extremely atrophic, weighing 60 gm., with the glandular elements replaced by fibrous tissue.

Comment.—The fatal infection with P. vulgaris followed prolonged terramycin treatment. For the three previous years, penicillin and penicillin-streptomycin aerosols had been administered, without P. vulgaris appearing on culture of the sputum.

Case 8.—A man aged 59 first had cough and increasing shortness of breath 14 years prior to admission. For two years prior to admission abundant yellowish, purulent sputum and increasing dyspnea kept the patient at home, and for the previous three months confined to a chair. On admission he was severely dyspneic and cyanotic. Sibilant, sonorous, and moist rales were heard throughout both lungs. Costal and nuchal muscles were involved in respiration, with paradoxical inward, upward displacement of the diaphragm during inspiration. The sputum contained many pus cells and on culture yielded a Streptococcus of the viridans type. The patient was short of breath after even a few words of conversation. A roentgenogram revealed diffuse bilateral pulmonary fibrosis and emphysema, involving chiefly the upper two-thirds of the right lung. Terramycin was administered for seven days, 500 mg. intravenously and 500 mg. by mouth daily. This was followed by administration of chloramphenicol, 2.5 gm. by mouth, and of streptomycin, 1 gm. intramuscularly, for 10 additional days. Improvement was rapid and conspicuous. The expectoration was reduced to 1 teaspoonful (15 cc.) and was white; Streptococcus of the viridans type was found on culture. The stools showed a heavy growth of Candida. Diaphragmatic breathing was then taught to the patient and pneumoperitoneum instituted. The patient was discharged greatly improved and able to walk down the corridor without difficulty. Increasing cough began at home four weeks later, and he was readmitted to the hospital two months after discharge *in extremis*. He was severely dyspneic, cyanotic and in a comatose state. The pulse was imperceptible; coarse, moist rales were heard throughout both lungs. The patient died of pulmonary edema three hours later. Autopsy confirmed the clinical diagnosis of pulmonary fibrosis, bullous emphysema, and bronchiectasis. The right atrium was dilated and the right ventricle hypertrophied. Culture of the lung tissues revealed P. vulgaris and Esch. coli.

Comment.—The remarkable improvement on treatment with the broad-spectrum antibiotic proved to be temporary. The patient, who lived out of town, arrived at the hospital at a time when effective treatment was no longer possible. The finding

of P. vulgaris in the culture of the lung tissue suggested that this resistant organism developed after the period of treatment with the broad-spectrum antibiotics, since it was not present on numerous cultures on admission and during treatment.

CASE 9.—A girl aged 14 contracted pertussis and bronchopneumonia at the age of 3 weeks, and from then on had suffered from repeated episodes of respiratory infections. During the two years prior to her first admission, in July, 1950, increasing dyspnea, cough, and small amounts of purulent expectoration were accompanied by a conspicuous deterioration in her physical well-being. During three months prior to culture studies made at the hospital the patient received the sulfonamides, without benefit, and courses of penicillin and chloramphenicol, with distinct but temporary improvement. Sputum cultures then revealed K. pneumoniae and Ps. aeruginosa, which appeared to be sensitive to terramycin, in a dose of 0.78 γ per cubic centimeter for K. pneumoniae and 1.56 γ per cubic centimeter for Ps. aeruginosa. Examination of the lungs revealed scattered crepitant rales throughout both sides of the chest. On x-ray examination an extensive fibrosis and bullous emphysema of both lung fields were noted, with patchy areas of pneumonitis.

A course of 8.5 gm. of terramycin over a five-day period resulted in marked, but temporary, decrease in cough and expectoration. Four weeks later the patient was given an additional course of terramycin, followed by chloramphenicol, which was found to inhibit K. pneumoniae, 1.9 γ per cubic centimeter. Improvement was marked, with decrease in cough and dyspnea. During the following nine months attempts were made to control infection with courses of penicillin, streptomycin, terramycin and aureomycin; but clinical improvement was maintained only on continued employment of chloramphenicol, 1.5 to 2 gm. daily, which the patient received for the greater part of six months. Although the dyspnea and cough finally increased, the patient was able to expectorate relatively small amounts of purulent sputum, which on culture generally revealed K. pneumoniae, and Ps. aeruginosa at times. With the development of increasing cough and dyspnea, she died during the final hospitalization, of 72 hours, in respiratory failure.

At necropsy, the smaller bronchi were noted to be distended with pus, with scattered areas of consolidation. Advanced bilateral bronchiectasis and numerous emphysematous blebs were present. Sputum cultures before death showed Ps. aeruginosa and K. pneumoniae, and cultures of the lung revealed Ps. aeruginosa, M. pyogenes var. albus, and nonhemolytic streptococci. A slight amount of free peritoneal fluid was found, from which Ps. aeruginosa, M. pyogenes var. albus, and nonhemolytic streptococci were cultured. Cultures of the heart's blood yielded M. pyogenes albus.

Comment.—Sputum cultures before antibiotic treatment were not obtained, but at the onset of treatment in this hospital Ps. aeruginosa and K. pneumoniae were found on culture. Although at first improvement was maintained with chloramphenicol, death took place finally, the infection being due to resistant organisms, especially Ps. aeruginosa, which was cultured from the lungs and peritoneal fluid at autopsy. The failure of the patient to eliminate large amounts of thick, greenish pus from the smaller bronchi was apparently related to an ineffective cough. The need for further investigation of methods of antibiotic therapy in the control of highly resistant organisms in chronic respiratory infection was clearly evident by the progression of disease in this patient.

CASE 10.—A man aged 64 was first admitted in 1948 for virus pneumonia, which responded promptly to aureomycin. In May, 1949, night sweats and a low-grade fever did not appear to diminish on treatment with aureomycin, but his temperature gradually returned to normal in three weeks. In August, 1949, night sweats, cough, and general malaise recurred. He was readmitted with a temperature of 103 F., and moist rales were heard over the right lower lobe. A palpable spleen and clubbing of the extremities were noted. The white blood cell count was 30,500. X-rays showed pneumonia in the upper and lower lobes of the right lung. Although his fever responded to chloramphenicol, severe anemia rapidly developed. Repeated chest films

showed some clearing, but there was evidence of chronic fibrosis. He remained fairly well for approximately one year and then was readmitted in September, 1950, for fever of six weeks' duration. At this time the lungs were clear, but the liver and spleen were palpable. The hemoglobin was 6.3 gm. per 100 cc.; the red cell count was 2,100,000, and the white cell count 1,000, with 6% myelocytes and 86,000 platelets. He was given cortisone over a two-week period, with no effect. One month later he had a temperature of 104 F., with signs of consolidation of the right upper lobe. Biopsy of the bone marrow showed a picture typical of acute myeloid leukemia. X-rays of the lungs showed diffuse mottling; the patient's course was rapidly downhill, and he died.

Necropsy revealed very extensive hemorrhagic lobular pneumonia. Histologically, numerous hyphae of the Aspergillus type were found in one lung section. Another unusual feature of this section was extensive endarteritis obliterans, seen in some of the larger arterioles traversing the areas of pneumonia. There were extensive areas of tissue necrosis. In other sections, taken from the spleen and liver, normoblasts and myeloblasts were present in abundance. The final diagnosis was myeloid leukemia, and lobar pneumonia with secondary infection due to aspergillosis.

Comment.—The pathologist, in discussing this case, stated: "The pulmonary aspergillosis is reasonably sure to have been a complication, one that we have seen recently in a few patients who have received large amounts of antibiotic agents, although I do not know whether there is any connection."

CASE 11.—A man aged 68 was admitted to the hospital in May, 1949, with a one-year history of weakness, anorexia, and swelling of the abdomen, and shortness of breath and cough of two years' duration, productive of 1 oz. of white, and at times mucopurulent, sputum. The diagnosis of cirrhosis and chronic bronchitis was made. He was readmitted in September, 1950. Paracenteses were required. Pulmonary function tests revealed a marked impairment in ventilatory function. The diagnosis was bronchiectasis with pulmonary emphysema and fibrosis. Repeated examinations of the sputum revealed pus, with cultures yielding K. pneumoniae.

Terramycin, 2 gm. daily in divided doses, was administered for seven days. On the third day following onset of terramycin therapy, he complained of abdominal pain and diarrhea, and the following day cultures of both sputum and stools showed many colonies of a Cryptococcus organism. No clinical improvement was noted in the cough or on examination of sputum. On April 8 the patient lapsed into coma and died within 24 hours.

Necropsy revealed many areas of emphysema and a mild degree of bronchiectasis in the lower lobes of both lungs. The peritoneal surfaces were covered with flecks of fibrin. There was 5,000 cc. of seropurulent fluid in the peritoneal cavity. The liver presented a shrunken, nodular appearance with the histological picture of postnecrotic cirrhosis. Direct smears from the lung and peritoneal fluid yielded large numbers of yeast-like organisms, which on culture proved to be a Cryptococcus. The final diagnosis was chronic bronchitis, bronchiectasis, and pulmonary emphysema; postnecrotic cirrhosis, and fibrinous peritonitis, with secondary infection due to cryptococcus.

Comment.—Infection of the lungs and the peritoneum with yeast organisms took place after seven days' treatment with terramycin in a patient whose resistance was apparently lowered by cirrhosis of the liver. Peritonitis, due to Cryptococcus, was the evident cause of death.

CASE 12.—A man aged 68 was admitted to the hospital complaining of pain in right calf of one month's duration and a hacking, nonproductive cough. Four days before admission the cough increased in severity and was accompanied three days later by chest pain, dyspnea, and yellowish-green sputum. The patient was found to be dyspneic and slightly cyanotic. Fine rales were heard at the right infracapsular and axillary areas. The temperature 101.8 F. There was a hard, fixed left supraclavicular lymph node.

On admission a roentgenogram of the chest revealed a right pleural effusion and an area of density in the right lower lung field. The patient was treated for thrombophlebitis and pulmonary infarction with heparin and bishydroxycoumarin. The sputum was purulent, and culture yielded a Streptococcus of viridans type. He was first given 800,000 units of crysticillin®

(crystalline procaine penicillin G) daily for 12½ days. With the persistence of pus in the sputum, terramycin, 2 gm. daily, was administered for seven days, in addition to crysticillin.* One week later, after a cystoscopy and retrograde pyelography, a shaking chill occurred; during the following week P. vulgaris was cultured from the urine and the blood. The organism was insensitive in vitro to terramycin, chloramphenicol, streptomycin, and aureomycin; however, 3 units of neomycin inhibited its growth. During the subsequent three weeks the patient received a total of 59 gm. of terramycin (2 to 4 gm. daily), 39 gm. of streptomycin (2 gm. daily), 5 gm. of aureomycin (2.0 gm. daily), 4 gm. of chloramphenicol (3 gm. daily) and 10 gm. of sulfadiazine (4.0 gm. daily). During this three-week period his fever spiked daily between 102 and 104 F.; three cultures of the urine and 14 cultures of the blood contained P. vulgaris. Three and a half grams of neomycin was given over a five-day period, after all other antibiotics had been discontinued, but it failed to induce any improvement and the patient died. Biopsy of the supraclavicular node revealed neoplastic changes, probably renal in origin.

Comment.—This case illustrates the development of a fatal P. vulgaris infection of the blood stream following the addition of terramycin to penicillin therapy. The culture of urine revealed P. vulgaris. Instrumentation of the urinary tract should also be considered an etiological factor in the P. vulgaris infection.

CASE 13.—A man aged 51, since the age of 39 had rheumatoid arthritis, of gradually progressive severity, producing considerable crippling. He received four courses of corticotropin and two courses of cortisone for this condition over a period of two years, with prompt remission of symptoms and signs on each occasion. At the age of 42, after several severe respiratory infections, he had onset of a chronic cough productive of large quantities of green, foul sputum. In February, 1951, pain developed in the right chest, associated with an increase in cough, productive of larger quantities of yellow sputum. He was admitted for antibiotic treatment and received 2 gm. of streptomycin and 800,000 units of penicillin daily for four days. The diagnosis of bronchiectasis was made by x-rays on that occasion. Sputum culture revealed streptococci of the viridans type before and after treatment.

In May and June he was followed at the clinic because of increasing dyspnea and cough productive of purulent sputum. Culture of the sputum revealed Type VI pneumococci and occasional Ps. aeruginosa. A course of 2 gm. of chloramphenicol daily for four days resulted in a slight reduction of sputum. During the subsequent three weeks the patient's cough increased; he became febrile and severely dyspneic, his condition necessitating admission to the hospital. He received 800,000 units of procaine penicillin G daily for four days, followed by 2,000,000 units of neo-penil* daily for seven days. Streptomycin, 2 gm. daily, was administered concomitantly for eight days. He also received 1 gm. of terramycin daily, in part intravenously and in part orally, for five days. Sputum cultures revealed P. vulgaris on one occasion and Ps. aeruginosa on two occasions during that period. The patient's course continued rapidly downhill, and he died.

On postmortem examination the bronchi and trachea were seen to contain a considerable amount of purulent sputum. Lung section showed innumerable small vesicles, representing dilated and ruptured alveoli. The bronchial tree was dilated. The central portion of the right lung and the lower lobe of the left lung were grayish-white and firm. Smear culture of material from the affected areas revealed yeasts, Gram-positive diplococci, and chromogenic Gram-negative rods.

Comment.—Resistance to infection due to administration of cortisone was in all likelihood an influential factor in the development of the fatal pulmonary infection, which was, nevertheless, characterized by the growth of unusual resistant organisms.

Case Reports

OBSERVATIONS ON THERAPY OF CYSTINE CALCULUS DISEASE

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A CYSTINE calculus represents a chemical precipitation of a definite crystalloid, cystine, $(S.CH_2.CH[NH_2].COOH)_2$, when its concentration in solution passes a certain critical level. The solubility of cystine has been determined by previous chemical studies.[1] Figure 1 depicts the solubility of cystine at various pH levels, according to Sano. Figure 2 indicates the solubility change with temperature.

Reference to the solubility curves shows that at pH 7 cystine will be held in solution up to a concentration of 16.2 mg. per 100 at body temperature, but at pH 8 35.3 mg. per 100 cc. can be held in solution.

The urinary cystine excretion in normal persons varies from 0.8 to 84 mg. a day.[2] A patient with cystinuria excretes 400 to 1,000 mg. per day. The urine of such persons may or may not be supersaturated with cystine, depending upon the urinary volume and pH. This explains why not all persons with cystinuria form recognizable calculi.[3] For example, with the urinary output of 2,000 cc. a day at pH 8 there could be held in solution 705 mg. of cystine. With the average urinary output of 1,500 cc. at pH 7 only 243 mg. of cystine could be held in solution. This is far less than the amount of cystine which the average person with moderate cystinuria would put out daily. If the urine is acid, solubility is still less and calculus formation may be anticipated.

In an effort to determine whether cystine in calculi follows the same solubility curve as free cystine, the calculi from the case to be discussed were analyzed by x-ray-diffraction studies [4] and by chemical methods. They were found to be com-

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4. Feitelly, G.: Personal communication to the authors (Physics Laboratory, The Mount Sinai Hospital, New York, Report 492, 1951).

posed of pure cystine. The solubility of cystine held in the calculi was determined by immersion in buffered solutions at pH levels of 6.0, 6.5, 7.0, 7.5, and 8.0, respectively, for two weeks (Fig. 1). The pH of these solutions was determined with the Beckman pH meter. The weights of the stones were determined before and after immersion and after thorough desiccation. The difference in weight before and after immersion was considered to be the amount dissolved. This amount was converted

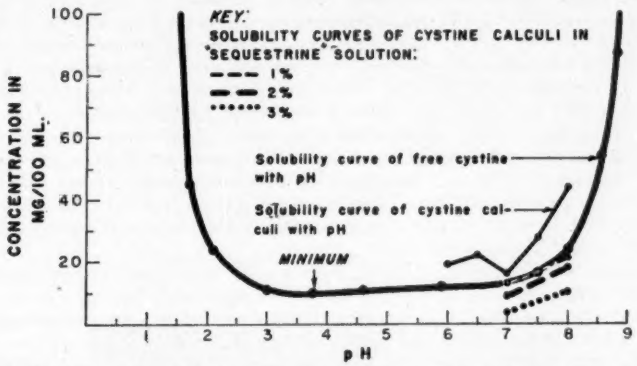

Fig. 1.—Solubility of *l*-cystine, in milligrams per 100 cc., and cystine calculi as altered by pH at 25 C.

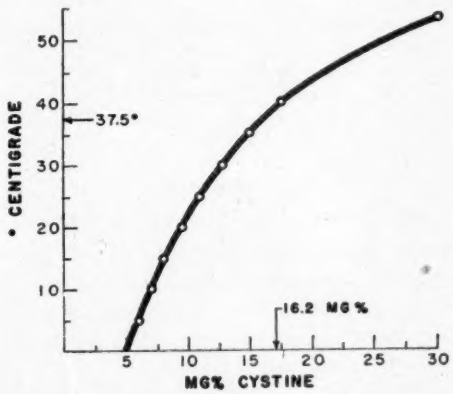

Fig. 2.—Variation in solubility of *l*-cystine in milligrams per 100 cc. with temperature, at pH 7.

to milligrams per 100 cc. and a solubility curve plotted. Reference to Figure 1 will show that cystine in calculi follows a solubility curve similar to that of free cystine. This is the most important factor to be considered in the clinical management of this disease.

Recently, Suby [5] suggested testing the solubility of cystine calculi in ethylenediamine tetraacetic acid ("sequestrine") solution. Therefore, the experiments were

5. Suby, H. I.; Albright, F.; Wayne, J., and Dempsey, E.: Dissolution of Urinary Calculi: Experiments with Ethylene Diamine Tetra-Acetic Acid With and Without a "Wetting Agent," J. Urol. **66**:527-532, 1951.

repeated, and weighed calculi were immersed in solutions of sequestrating agent at various pH levels. Reference to Figure 1 will show that in our experiments the solubility of cystine is decreased by the addition of ethylenediaminetetraacetic acid in solution.

REPORT OF A CASE

A young white man (Registry 5368), aged 22, was admitted to the Urological Service of the United States Veterans Administration Hospital, Brooklyn, on March 20, 1951, with a history of having passed calculi repeatedly since the age of 18. Examination of the urine revealed typical cystine crystals (Fig. 3). X-ray-diffraction and chemical studies of voided calculi confirmed the diagnosis. The patient was treated prior to admission with a cystine-poor diet and alkalization of the urine. After three years of such therapy and after having passed 237 calculi (Fig. 4), he was referred to the hospital for further studies.

At the hospital the calculi were visualized in the lower calyces of the left kidney (Fig. 5). Intravenous and retrograde pyelography demonstrated normal renal function and morphology except for the calculi (Fig. 6). An analysis of the patient's familial history did not reveal other persons with cystinuria among either parents or siblings, nor did examination of their urines reveal any cystine crystals. This is unusual, as there is generally a marked familial background in this metabolic disturbance.

To evaluate the extent of the patient's metabolic error, daily urinary cystine excretion was determined. To achieve this end, the Sullivan method was modified for use with the spectrophotometer. The concentration of the agents required was altered, and a wavelength of 520 $m\mu$ was selected by trial and error. Briefly, the procedure was as follows: 2.5 cc. of urine was diluted with an equal amount of distilled water, after which 2 cc. of a 5% sodium cyanide solution was added, and the solution was left standing for 10 minutes. One cubic centimeter of a 0.25% solution of sodium 1, 2, naphthoquinone-4-sulfonate was added, and the solution was agitated for 10 seconds. An additional 5 cc. of 10% sodium sulfite in 0.5 N sodium hydroxide was added, and the solution was allowed to stand for 30 minutes. One cubic centimeter of 2% sodium thiosulfate in 0.5 N sodium hydroxide solution was then added, and after thorough mixing the color was read against a standard cystine solution. The method will be described in greater detail in another report.[6]

The average excretion of urinary cystine by our patient on 15 consecutive daily analyses was 890 mg. per 24 hours, ranging from 340 to 1,660 mg. per 100 cc.

THERAPY

In the past recommended treatments for cystinuria have included the following:

Low-cystine diet or low-sulfur diet

Choline administration as recommended by Zinsser[7]

Cortisone and corticotropin (ACTH) therapy (These drugs have never been used in treatment of this condition and will be described in the following report.)

Ascorbic acid therapy as described by Rolnick[8]

Alkalization of urine and maintenance of a high urinary volume output

Low-Cystine Diet.—As will be seen from the chart taken from Zinsser's paper (Fig. 7), cystine is a reduction product of cysteine, which is a conversion product of methionine, which, in turn, is an essential amino acid and, therefore, should not

6. Tabenkin, P. A., and Weinberg, S. R.: The Spectrophotometric Determination of Cystine in the Urine: Modification of Sullivan Reaction, to be published.

7. Zinsser, H. H.: The Effect of Oral Choline in Reducing Cystine Excretion in Cystinuria: A Report of 2 Cases, J. Urol. **63**:929-935, 1950.

8. Rolnick, H.: The Practice of Urology, New York, J. B. Lippincott, Co., 1949, Vol. II, p. 801.

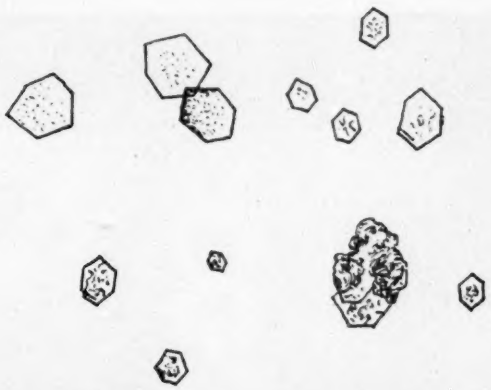

Fig. 3.—Cystine crystals as seen in urine (artist's sketch).

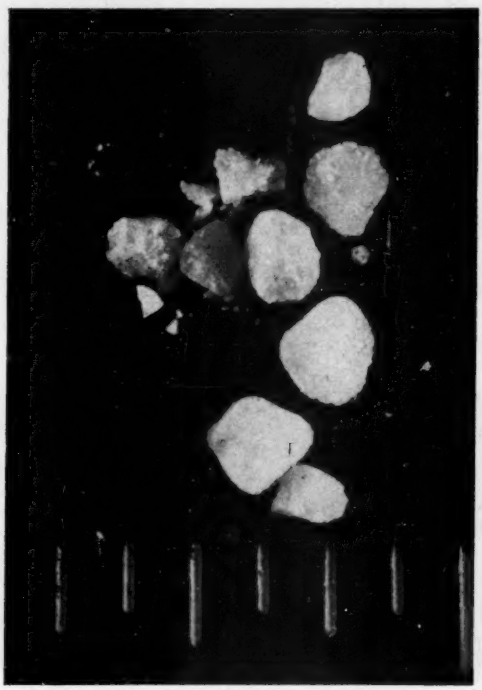

Fig. 4.—Cystine calculi passed spontaneously.

Fig. 5.—Plain roentgenogram showing cluster of calculi in lower pole of left kidney.

Fig. 6.—Retrograde pyelogram showing normal morphology except for cluster of calculi in lower pole of left kidney.

be eliminated from the diet. Radioisotope studies by Tarver and Schmidt [9] have shown that in the cystinuric animal cystine is more rapidly formed from methionine and excreted as cystine than in a normal dog. When labeled methionine is injected in small doses into normal or cystinuric dogs, only 4% or less is excreted as such in the urine, the remainder being synthesized into body protein. Therefore, as the main source of cystine is endogenous, reduction of the amount of exogenous cystine- or sulfur-containing compounds will not reduce the degree of cystinuria.

Choline Therapy.—The rationale for choline therapy is to attempt to prevent the formation of insoluble cystine by effecting a more perfect biochemical conversion of methionine to cysteine with the use of the labile methyl group from choline. The

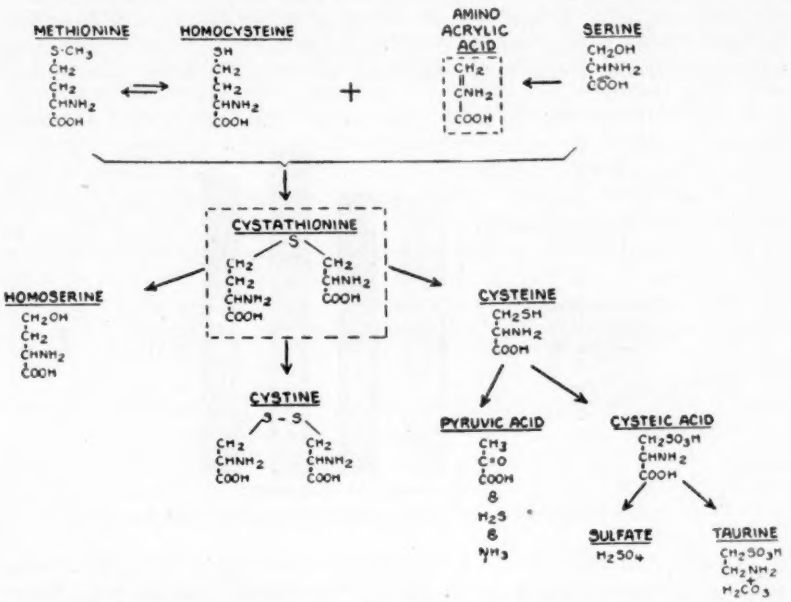

Fig. 7.—Theoretical biosynthesis of cystine (Figure 2, p. 931, in article by H. H. Zinsser, published in *Journal of Urology*, Baltimore, The Williams & Wilkins Company, 1950).

biosynthesis of labile methyl groups was recently summarized in an editorial in *The Journal of the American Medical Association.*[10] Here it is shown that when the heavy hydrogen content of the body water is increased, the methyl group in choline prepared from these tissues contains heavy hydrogen, an indication of the in vivo synthesis of the methyl group. This work has been confirmed by feeding labeled simple carbon compounds and finding labeled methyl complex compounds in the organism.[11] This would indicate no lack of choline synthesis in the normal

9. Tarver, H., and Schmidt, C. L. A.: The Urinary Sulfur Partition in Normal and Cystinuric Dogs Fed Labeled Methionine, J. Biol. Chem. **167**:387-394, 1947.

10. The Biosynthesis of Labile Methyl Groups, Editorial, J. A. M. A. **147**:1672, 1951.

11. Du Vigneaud, V., and others: On Carbon Compounds in the Biosynthesis of the Biologically Labile Methyl Group, J. Am. Chem. Soc. **73**:2782-2784, 1951.

subject and, therefore, no need for choline administration except possibly in subjects with marked liver damage. Zinsser has reported reduction in the amount of cystinuria in two cases after 250 mg. of choline hydrochloride daily was added to the diet. However, in both these cases the cystine output was less than 400 mg. in 24 hours, and the reductions were within the fluctuations to be expected in cystine excretion, as noted in our experiments.

Our patient was given 1 gm. of choline a day in addition to the regular hospital diet, starting Oct. 30, 1951. Daily examinations were made of the cystine excretion until Nov. 30, 1951. Whereas before receiving choline the patient passed an average of 890 mg. of cystine in 24 hours, after choline administration the average excretion was 910 mg. for 24 hours. In this experiment, as noted above, 27 consecutive determinations were made. In view of reports of hepatic damage due to cystine deposition in the liver or alteration of protein metabolism, liver-function tests were performed, with normal results. Hematologic studies done on numerous occasions were normal.

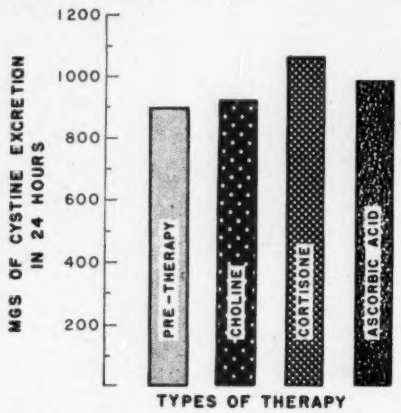

Fig. 8.—Effect of drugs used to alter urinary cystine excretion.

Ascorbic Acid Therapy.—Levine (cited by Rolnick [8]) has promulgated a theory that the formation of cystine may be diminished by ascorbic acid, which is a strong reducing agent and which will favor the synthesis of cysteine. The patient was, therefore, given 300 gm. of ascorbic acid three times a day in order to achieve full saturation of the tissues with vitamin C. Ten consecutive daily determinations showed an average excretion of 965 mg. per day, indicating that ascorbic acid in our experiments did not hinder the formation of cystine.

Cortisone and Corticotropin.—Cortisone and corticotropin have marked effect on protein metabolism in that they increase the excretion of nitrogenous products. Thorn [12] is of the opinion that the increased uric acid excretion seen during cortisone therapy is due mainly to an alteration in the renal clearance of uric acid. Inasmuch as cystine is formed universally in the organism, cortisone was expected to have general effect on either its synthesis or its excretion. The patient was given cortisone therapy, 50 mg. per day, starting Dec. 11, 1951, and continuing until Jan. 14,

12. Thorn, G. W., and others: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783-793, 1950.

1952. During this time, the urinary excretion of cystine was studied daily and 31 determinations were made. In each determination the total urinary volume and pH of the urine were carefully noted. It was found that on an average the patient had an excretion of 1.055 gm. of cystine a day, so that cortisone did not block the formation of cystine in the cells but increased its excretion by the breakdown of proteins or by a decreased renal threshold for cystine. Only toward the termination of the patient's course of cortisone on Jan. 12, 1952, did he pass any calculi. We are at a loss to explain these findings except that a greater amount of cystine might have been held in solution, as evidenced by its higher excretion.

Improving Solubility.—Fluids were forced to increase the urinary volume, and urinary alkalization was attempted, in order to keep as much cystine as possible in solution. Potassium citrate in divided doses of 1 gm. five times a day with a dose at 2 a. m. was employed to alkalize the urine. The nocturnal dose [13] was given to maintain alkalization throughout the night. The urinary pH was determined by the patient on freshly voided urine before each meal, at bedtime, and at 2 a. m. using "pHydrin" paper (chemical indicator, bromothymol blue),[13a] instead of the customary nitrazine paper. With this paper, the finer gradations of pH can be determined with greater ease: At pH 6 the color is yellow, at pH 6.5 olive, at pH 7 light green, at pH 7.5 dark green, at pH 8 a definite blue. The patient's readings with this paper were checked on 10 different occasions with the Beckman glass-electrode pH meter, and the results were verified within 0.01%. It will be recalled that at pH 8 the solubility of cystine at body temperature is 35.3 mg. per 100 cc. Inasmuch as our patient was excreting approximately 900 mg. of cystine, he required a urinary volume of at least 2,500 cc. at pH 8 to keep the cystine in solution. A urinary output of 2,500 or 3,000 cc. a day is very difficult to maintain, and it is also difficult to keep the urinary pH uniformly at 8. Under ideal conditions, if these conditions could be maintained no further development of cystine calculi should be expected.[14] Our patient was maintained on such a regimen for three months; during this time he passed only three small calculi, and it is our impression that the density of the urinary calculi appeared to be diminished on x-ray examination.

SUMMARY

A case of cystinuria with calculus formation is reported in which various forms of therapy were attempted.

Choline, cortisone, and ascorbic acid therapies were found to be of no effect. Corticotropin (ACTH) or cortisone probably increases the renal clearance of cystine.

Maintenance of urinary volume and pH at levels which keep cystine in solution seems to be effective. The rationale for this therapy is discussed.

Not all persons with cystinuria can be treated similarly; the level of cystine excreted by each patient should be determined by accurate quantitative studies, and treatment should be individualized.

575 Ocean Ave. (26) (Dr. Weinberg).

13. The 1950 Year Book of Urology, edited by W. W. Scott, Chicago, The Year Book Publishers, Inc., 1951, p. 55 (editorial comment).

13a. Supplied by the Micro-Essential Laboratory, 3005 Ave. K, Brooklyn 10.

14. Crowell, A. J.: Cystine Nephrolithiasis: Roentgenographic Demonstration of Disintegration by Alkalinization, Surg., Gynec. & Obst. **38**:87-91, 1924.

BACTERIAL ENDOCARDITIS DUE TO SALMONELLA SP. (TYPE SENDAI) WITH RECOVERY

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AND
HUANG CHI-TO, M.D.
HONG KONG

BACTERIAL endocarditis due to organisms of the Salmonella group is relatively rare. Stumpe and Baroody [1] reviewed in this journal the literature for the period 1930 to 1950 and found 21 cases recorded. They referred to four unpublished cases to which their attention had been drawn and reported one further case. We are not aware of any other case report since that communication. All these 26 cases terminated fatally. Since the introduction of chloramphenicol, De Swiet [2] and Stumpe and Baroody [1] each have reported its use in one case. In neither case was the course of the disease influenced.

The purpose of this paper is to report a case of bacterial endocarditis due to Salmonella sp. (Type Sendai) with recovery following combined penicillin and chloramphenicol therapy.

REPORT OF CASE

History.—Mrs. G., aged 29 years, a primipara six months pregnant, was admitted to the University Department of Medicine, Queen Mary Hospital, on Jan. 6, 1952, with a complaint of repeated rigors and fever of six days' duration.

For some two weeks she had been generally unwell and had felt feverish especially toward the evening. She had intermittent, moderately severe attacks of headache, with associated nausea, anorexia, and vague abdominal discomfort. These symptoms were attributed to the pregnancy. Six days before admission she had a rigor which was followed by severe aching pains in the bones, frontal headache, and marked general malaise. The rigors recurred at frequent but variable intervals until her admission to the hospital. In the four days before admission the tips of the fingers and toes were painful, and she noticed red spots on her neck and forearms. On the morning of admission there was sudden, severe left subcostal pain which was aggravated by deep inspiration.

Her last menstrual period was in June, 1951, and she had been attending the Department of Obstetrics and Gynaecology for antepartum care. At no stage of her attendance was any abnormality detected on routine systemic examination.

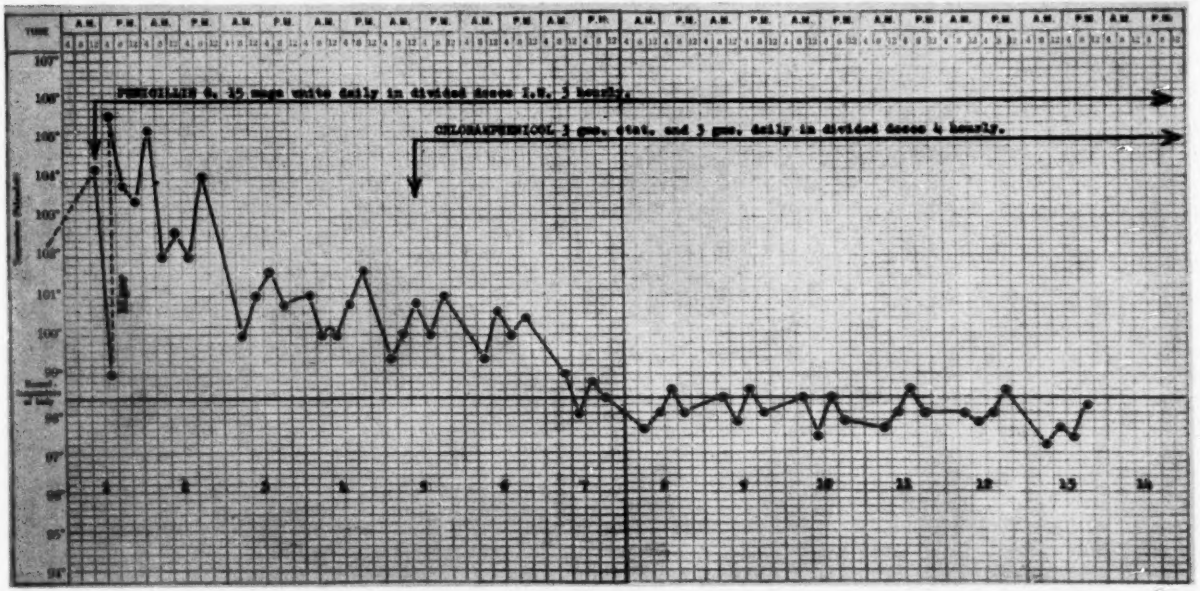
She had always enjoyed good health and had been examined from time to time by competent physicians, who had found no organic disease.

Physical Condition on Admission.—The patient was a well-nourished, well-developed, pale European woman who was manifestly acutely ill. Multiple petechiae were present on the neck, the palpebral conjunctivae, and both forearms. Ophthalmoscopic examination showed two boat-shaped hemorrhages in the right retina. The tips of three fingers and two toes were tender. There was no clubbing. Her temperature was 104.2 F.

From the Departments of Medicine and Pathology, University of Hong Kong.
Dr. McFadzean is Professor of Medicine, and Dr. Huang is Lecturer in Bacteriology.

1. Stumpe, A. R., and Baroody, N. B.: Salmonella Endocarditis, A. M. A. Arch. Int. Med. **88**:679 (Nov.) 1951.

2. De Swiet, J.: Subacute Bacterial Endocarditis Due to Salmonella Typhi-Murium, Brit. M. J. **2**:1155 (Nov. 19) 1949.



Temperature chart showing response to penicillin and to chloramphenicol in early phase of treatment. *Mega unit* is 1,000,000 units.

The pulse rate was 136 per minute, with occasional extrasystoles. Her blood pressure was of the order of 120/60. The apical impulse was in the fifth intercostal space just without the midclavicular line. A purring systolic thrill was felt over the base of the heart, and on auscultation a harsh systolic murmur was present which was maximal over the aortic area and extended into the vessels of the neck. Down the left border of the sternum there was a soft diastolic murmur best heard in the third intercostal space.

The uterus was enlarged to a degree consistent with a six months' pregnancy. Fetal movements were felt, and the fetal heart was heard. The spleen was palpable 2 cm. below the costal margin and was tender. No rub was heard.

Examination of the remaining systems showed no abnormality.

Laboratory Findings on Admission.—The urine contained albumin (2+), and on microscopic examination numerous red blood cells and occasional blood and cellular casts were seen. The white cell count was 12,200 per cubic millimeter, with 79% polymorphonuclear cells, 20% lymphocytes, and 1% monocytes. The red cell count was 3,700,000 per cubic millimeter, and the hemoglobin concentration was 9.7 gm. per 100 cc.

Progress.—Three cultures of peripheral blood and one of sternal marrow were made. In view of the severity of her symptoms 15,000,000 units of penicillin G per day was given in divided doses every three hours. There followed a marked improvement in the patient's general condition. The rigors ceased, and within 48 hours the temperature was greatly reduced, although there was still significant fever (Chart). After the first 24 hours no further petechiae occurred. The heart murmurs and the size of the spleen remained unchanged.

On the fifth day after the start of treatment there was reported the isolation from one blood culture and from the sternal marrow culture of an unidentified member of the Salmonella group. In the light of this report the treatment was reviewed. It was considered unwise to discontinue the penicillin therapy because of the apparent response. Chloramphenicol was given in addition by mouth, 3 gm. at first and thereafter 3 gm. per day in divided doses every four hours. Within 48 hours the patient was apyrexial and remained so thereafter. Three days after the start of chloramphenicol therapy the spleen could not be felt, and red blood cells and casts were no longer present in the urine. Five days later the palpable thrill had disappeared, the systolic murmur had lost its harsh character, and the diastolic murmur was no longer detected. The erythrocyte sedimentation rate progressively fell, and on the 21st day of treatment it was within normal limits.

Penicillin and chloramphenicol administration was discontinued on Feb. 2, which was 26 days after the start of penicillin and 23 days after the start of chloramphenicol therapy. The total doses of penicillin and chloramphenicol were 420,000,000 units and 72 gm., respectively.

She was discharged from the hospital on Feb. 19, 1952, and was seen at intervals for four months after discharge, until June 12. In this period she remained apyrexial and well. One month after discharge, the systolic murmur was no longer heard and systematic examination revealed no abnormality.

On April 28 she was delivered of a normal full-term child by a Caesarean section which was necessitated by purely obstetrical considerations.

BACTERIOLOGICAL STUDIES

Forty-eight hours' incubation yielded a growth in the sternal marrow culture and in one peripheral blood culture of Gram-negative, non-spore-forming, motile bacilli having the morphology found in young cultures of Salmonella typhi. Subculture on MacConkey's medium revealed a pure growth of nonlactose fermenters in each case.

The biochemical reactions are set forth in the accompanying table.

The organism was agglutinated by Salmonella paratyphi A O and H sera, and by Salmonella paratyphi C H serum. The patient's serum, taken at the end of the second week after admission, agglutinated the organism with an O titer of 1:80 and an H titer of 1:640. When the patient's serum was absorbed by S. paratyphi A and S. paratyphi C cultures, respectively, the absorption was not complete, for a positive agglutination took place when each specimen of absorbed serum was tested against the isolated organism. A control series using the organism isolated for absorption resulted in the absorption being complete.

From the results of the biochemical tests and in view of its cross reaction serologically with S. paratyphi A (I,XII: a) and S. paratyphi C (1,5) sera, the culture isolated was considered to be Salmonella sp. (Type Sendai).

The culture was sent to Dr. Joan Taylor, of the Salmonella Reference Laboratory, London, for final identification. Dr. Taylor [3] confirmed the antigenic formula of O = IX, XII; H = a — 1, 5, and identified the organism as Salmonella sp. (Type Sendai).

In consequence of the striking response of the patient's illness to penicillin therapy, an in vitro penicillin sensitivity test of the organism was carried out. The tube-test method [4] was employed. The sensitivity to penicillin G of the organism was 15.65 units per cubic centimeter and that of the control Staphylococcus pyogenes var. aureus (Heatley strain) was 0.03 unit per cubic centimeter.

Biochemical Reactions of the Isolated Organism

Reagent	Result Read or Tested, Days After Culture *		
	2	5	10
Dextrose	A g	A g	A g
Lactose	—	—	—
Mannitol	A g	A g	A g
Maltose	A g	A g	A g
Sucrose	—	—	—
Arabinose	A g	A g	A g
Dulcite	—	—	—
Rhamnose	A	A	A
Xylose	—	A	A
Kligler's iron agar			
Slant	No change	No change	X
Butt	A g	A g	X
Hydrogen sulfide	+	+	X
Indole	—	—	X
Nitrate	+	+	X
Methyl red	+	+	X
Voges-Proskauer	—	—	X
Gelatin	—	—	X
Urea	—	—	X
Stern glycerin broth	—	—	X
Motility (in semisolid agar)	+	+	X

* X indicates test not done; A, acid produced, and g, a bubble of gas produced. Minus sign means negative result, and plus sign, positive result.

COMMENT

The organisms isolated from the 25 cases of Salmonella endocarditis reviewed by Stumpe and Baroody [1] included Salmonella choleraesuis, Salmonella paratyphi B, Salmonella typhimurium, S. typhi, Salmonella fayed, Salmonella sp. (Type Thompson), and Salmonella sp. (Type Minnesota). In the case which these writers reported, endocarditis was due to Salmonella sp. (Type Oranienburg). It is of interest to note that 13 of the 26 cases were due to S. choleraesuis.

Salmonella sp. (Type Sendai) is one of the rarer species of Salmonella pathogenic to man. According to Topley and Wilson,[5] Salmonella sp. (Type Sendai) was first isolated from cases of enteric fever in Japan by Aoki and Sakai in 1925. Bornstein and Saphra [6] next identified the organism in a culture sent them for

3. Taylor, J.: Personal communication to the authors.

4. Kolmer, J. A.: Penicillin Therapy Including Streptomycin, Tyrothricin, and Other Antibiotic Therapy, Ed. 2, New York, D. Appleton-Century Company, Inc., 1947.

5. Topley, W. W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunity, Ed. 3, Baltimore, Williams & Wilkins Company, 1946.

6. Bornstein, S., and Saphra, I.: Occurrence of Unusual Salmonella Species, J. Infect. Dis. **71**:55 (July-Aug.) 1942.

identification from Georgia. The culture was obtained from the blood of a patient with an enteric-like fever on the eighth day of illness. These writers, however, refer to a personal communication from Dr. P. R. Edwards, who had identified this species in a culture obtained from a patient in Connecticut.

In producing gas, although the gas formed was never profuse, the present culture is in conformity with that reported both from the International Salmonella Centre, in Copenhagen, and by Bornstein and Saphra. The unusual feature of this culture is its production of hydrogen sulfide, which has not been previously reported. Kauffmann [7] maintains that Salmonella sp. (Type Sendai) does not produce hydrogen sulfide, while Salmonella sp. (Type Miami), which has the same antigenic formula as Salmonella sp. (Type Sendai), does. Nevertheless, the rapid fermentation of arabinose, the negative reaction in Stern's glycerin broth, as well as the negative reaction on ammonium citrate medium, readily distinguish our culture from Salmonella sp. (Type Miami).

In view of the subsequent findings, the history of fever, headache, and vague abdominal discomfort preceding the acute symptoms suggests a low-grade enteric fever. The acute symptoms coupled with the clinical findings on admission establish beyond reasonable doubt that there was a bacterial infection of the aortic valve.

The response to penicillin was dramatic and may well be explained by the dosage employed. The organism was shown in vitro to be sensitive to penicillin in a concentration of approximately 15 units per cubic centimeter. According to Clark,[8] Eagle, Fleischman, and Musselman reported that a single intramuscular injection of 1,200,000 units of penicillin G in man results in a serum level of 24 units per cubic centimeter after 30 minutes, 20 units after one hour, and 5 units after two hours. Since the patient received 1,900,000 units every three hours, it may be assumed that for at least one hour after each injection the serum concentration was above the in vitro sensitivity level. Furthermore, the in vitro sensitivity need not necessarily indicate the response in vivo. For example, in a recent case bacterial endocarditis due to an indifferent Streptococcus reacted satisfactorily to 3,000,000 units of penicillin per day, yet in vitro sensitivity tests showed the organism to be resistant to concentrations below 15 units per cubic centimeter.

SUMMARY

A case of bacterial endocarditis due to Salmonella sp. (Type Sendai) in a six months pregnant woman is described.

The biochemical and serological reactions of the organism are described, and the production of hydrogen sulfide in Kligler's iron agar is recorded.

Recovery and complete clinical resolution of the valve lesion followed the exhibition of penicillin and chloramphenicol. The response to penicillin alone was dramatic.

Major Peter Stewart, Royal Army Medical Corps, pathologist, assisted in identifying the organism. Dr. Joan Taylor established its identity.

7. Kauffmann, F.: The Diagnosis of Salmonella Types, Springfield, Ill., Charles C Thomas, Publisher, 1950.

8. Clark, A. J.: Applied Pharmacology, revised by A. Wilson and H. O. Schild, Ed. 8, London, J. & A. Churchill, Ltd., 1951.

PREGNANCY IN MYXEDEMA

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WILLIAM C. KEETTEL, M.D.
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MYXEDEMA in women is usually associated with altered menstrual function, infertility, or repeated abortion.[1] Parkin and Greene[2] described the occurrence of pregnancy in one patient with cretinism, in two with juvenile myxedema, and in three with adult myxedema. Their review of the world's literature revealed 10 previously recorded cases of pregnancy in true hypothyroidism, making a total of 16 cases.[3] Their methods of diagnosis included determinations of the basal metabolic rate and the serum cholesterol, the clinical appearance, and the response of the patient to thyroid extract. Myxedema cannot always be diagnosed unequivocally by clinical findings plus these laboratory aids. In the past, many, varied disorders of the female reproductive function unfortunately have been attributed to hypothyroidism on the basis of a single basal metabolic rate determination. We agree that the 16 previously reported cases represented true myxedema. One might expect that the increased accuracy of diagnosis made possible by determinations of protein-bound iodine of the blood plasma and radioactive-iodine-uptake studies would lead to recognition of a greater number of women with myxedema in whom pregnancy had occurred without thyroid therapy. No additional cases have been reported since Parkin and Greene's summary in 1943.

The purpose of this paper is to report a pregnancy in an unequivocally myxedematous woman whose symptoms were established and had persisted for a 15-year period, during which time she bore six children, four of whom are living today. During this time she had never taken thyroid substance. Studies of the mother and her four children comprise the present report.

From the Departments of Internal Medicine and Obstetrics and Gynecology, College of Medicine, University Hospitals, State University of Iowa.

1. (*a*) Davis, A. H., Jr.: Hypothyroidism and Pregnancy, J. Bowman Gray School Med. **5**:66, 1947. (*b*) Litzenberg, J. C., and Carey, J. B.: The Relationship of Basal Metabolism to Gestation, Am. J. Obst. & Gynec. **17**:550, 1929.

2. Parkin, G., and Greene, J. A.: Pregnancy Occurring in Cretinism and in Juvenile and Adult Myxedema, J. Clin. Endocrinol. **3**:466, 1943.

3. Audebert and Claverie: Grossesse chez une myxœdèmateuse, Bull. Soc. obst. et gynéc. Paris **10**:79, 1921. Fruhinsholz, A.: Grossesse et myxœdème, ibid. **14**:419, 1925. Howard, C. P.: Myxedema: A Study, J. A. M. A. **48**:1226, 1325, and 1403, 1907. Merguet: Schwangerschaft bei sporadischem Kretinismus, abstracted, Klin. Wchnschr. **1**:971, 1922. MacIlwaine, S. W.: Myxedema in Mother and Child, Brit. M. J. **1**:1261, 1902. Plummer, S. W.: Pregnancy Occurring in a Case of Myxedema, Univ. Durham College Med. Gazette **22**:58, 1921-1922. Townsend, C. W.: A Pregnant Cretin, Arch. Pediat. **14**:20, 1897.

CASE HISTORY OF MOTHER

The mother, a 25-year-old white woman, was born and raised in the goiter belt of Michigan. Her growth and development were apparently normal until the age of 10 years, and her record in school was "above average" until the fifth grade. At this time she began to note drowsiness in class, constant fatigue, and great difficulty with her schoolwork. From this time on, her scholastic performance declined, and she was forced to leave school at the age of 16 after failing the 10th grade twice. At about this time a nontender goiter developed, which grew smaller after "a year or two." Her voice had become deep and husky, her skin dry, and her hair coarse. She cannot recall ever having perspired, and she does not tolerate cold weather. Over the past 12 years she has been treated repeatedly for anemia with iron preparations, but without improvement.

Menstruation began at 16 years, was scanty, and recurred at fairly regular intervals of three months. This pattern of oligomenorrhea persisted to the time of her last pregnancy. She was married in 1944 at the age of 17. Data of her pregnancies and children are presented in Table 1.

Since her marriage, the patient has noted great difficulty in performing routine household tasks. Memory has been retarded, requiring the patient to write notes to herself in order to complete simple household tasks, such as washing dishes, making beds, or shopping for groceries.

Results of Physical Examination.—The patient was well nourished and small in stature (height, 5 ft. 1 in. [154.9 cm.]) and weighed 123 lb. (55.8 kg.). She was very slow in thought and

TABLE 1.—*Summary of Data on Children of Myxedematous Mother*

Initials	Date	Place of Birth	Sex	Birth Weight, Gm.	Comment
.....	1945	Michigan	F	1,020	Died first day
.....	1946	Michigan	F	2,640	Died at age 7 mo.; pneumonia
J. T.*	1947	Michigan	M	3,060	Living, but mentally dull
H. T.*	1949	Michigan	M	3,180	Living, normal except minor congenital defect
D. T.*	1951	Iowa	F	2,280	Living, but mongolian idiot
B. T.*	1952	Iowa	M	2,830	Living, apparently normal at 7 wk.

* Children included in this series.

movement. Her hair was black, lusterless, and coarse. Her skin was coarse, dry, and without lanugo hair. Eyes, ears, nose, and throat were normal, except for moderate hypertrophy of the faucial tonsils, far-advanced dental caries, and a thick blunt tongue. The thyroid was palpable but was considered normal. The voice was deep and husky, and her speech was slow. The heart was normal in size, activity, and contour, with a regular rate of 80, and the blood pressure was 120/70 mm. Hg. The abdomen revealed a gravid uterus extending to within 3 cm. of the xiphoid process. Fetal heart sounds were heard. The extremities were normal except for dryness of the skin, increased thickness of the subcutaneous tissues, and slow relaxation of the deep tendon reflexes. Alternate-motion rates of the tongue and hands were 25% of normal.

Antepartum studies before treatment with thyroid gave the following results: The basal metabolic rate was —12%. Protein-bound-iodine uptake was 2.8 γ per 100 cc. Cholesterol measured 500 mg. and cholesterol esters 320 mg. per 100 cc. Radioiodine uptake studies were not done because of pregnancy. The hemoglobin concentration was 10.0 gm. per 100 cc.

Treatment was begun with 60 mg. of desiccated thyroid daily, and 31 days later the patient delivered an apparently normal boy (B. T.). By this time her appearance and the alternate-motion rates were improved, and she noted subjective improvement. On the sixth postpartum day, further laboratory studies were done on the mother and child (Table 2). The mother, who had been taking 180 mg. of thyroid daily since her delivery, appeared markedly improved, her skin being moist and elastic and her mental acuity improved. For the first time she noted sweating.

TABLE 2.—*Results of Postpartum Studies on Mother and Child*

	Plasma Cholesterol, Mg./100 Cc.	Esters, Mg./100 Cc.	Protein-Bound Iodine, γ/100 Cc.	I^{131} Uptake, %	
				4 Hr.	24 Hr.
Mother	320	122	5.4	1	1
Child	Less than 50	...	7.4	12	15

Because the mother stated that her other children were "slow," arrangements were made to study them. Seven weeks post partum the mother and her four children were examined.

Fig. 1.—D. T., a child with mongolism.

CASE HISTORIES OF CHILDREN

J. T., a boy aged 4 years 9 months, had been slow to develop, did not walk until the age of 2 years, was toilet-trained at the age of 3½ years, and was unable to talk at the time of examination.

Results of Physical Examination.—His height, weight, and skull measurements were moderately below normal. His eyes showed prominent inner canthal folds, his teeth advanced caries, and his tonsils marked hypertrophy. The thyroid was normal in size. The heart and lungs were normal, except for a Grade II systolic murmur best heard in the third and fourth left intercostal spaces. The extremities revealed short fifth fingers bilaterally. The skin was moist and elastic.

H. T., a boy aged 2 years 11 months, sat up at the age of 1 year, walked at 2 years, and recently became toilet-trained, and able to feed himself. He spoke intelligibly.

Results of Physical Examination.—He appeared alert, but his height, weight, and skull circumference were slightly below normal. The remainder of the examination showed no abnormality except for slight dental malformations (double canine tooth) and an undescended left testis.

Fig. 2.—B. T., a normal newborn boy. There is no evidence of goiter.

Fig. 3.—Family picture. Mother was seven weeks post partum.

D. T., a girl aged 1 year 4 months, had always been retarded physically and mentally. She was unable to sit up or roll over and seldom cried. She had had frequent upper respiratory infections, and her mother had noted chronic mouth breathing.

Results of Physical Examination.—Height, weight, and skull measurements were far below normal. The anterior fontanel was open; the eyes were wideset, and the expression was stupid. There were prominent inner canthal folds; the nose was flat and poorly developed, and the tonsils were large. The extremities revealed small fifth fingers and bilateral clawfoot deformities.

B. T., a boy aged 7 weeks, had eaten poorly but had been alert and responsive. His height, weight, and skull circumference were below normal. The results of physical examination were normal except for diminutive size and poor nutrition.

Roentgenographic studies of the skulls, chests, and hands of all four children showed no significant abnormalities, except for retarded bone age, an open fontanel in D. T., and short fifth fingers of J. T. and D. T. (Table 3).

COMMENT

A review of our hospital records since 1938 failed to disclose any additional cases (aside from those reported by Parkin and Greene) of pregnancy in unequivocal hypothyroidism. In seven cases the possibility was considered, but in each instance conclusive evidence was lacking or the hypothyroidism had been recognized before the third month and specific therapy had been started.

The unusual occurrence of pregnancy in myxedema poses several questions:

What effect has the hypothyroid state of the mother on the child?

What effect has the pregnancy on maternal metabolism?

TABLE 3.—*Results of Clinical Studies on Children of Myxedematous Mother*

Child	J. T.	H. T.	D. T.	B. T.
Age	57 mo.	35 mo.	16 mo.	7 wk.
Bone age *	36 mo.	24 mo.	Newborn	Newborn
Urine	Normal	Normal	Normal	Normal
Blood:				
Hemoglobin, gm./100 cc.	11.0	11.0	11.0	12.0
Red cells, millions	3.40	4.00	3.95	4.40
White cells	9,800	10,900	9,900	12,500
Wassermann test	Neg.	Neg.	Neg.	Neg.
Protein-bound iodine, γ/100 cc.	10.0	9.1	7.1	10.7
Cholesterol, mg./100 cc.	119	240	165	91
Cholesterol esters, mg./100 cc.	82	134	100	57
I^{131} uptake, %:				
4 hr.	13	14	14	9
24 hr.	19	18	19	18
Psychological evaluation †	Moron	Dull normal	Idiot	Indeterminate

* Carpal bone age (Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937).
† Selected items from the Vineland Social Maturity Scale and Stanford-Binet tests.

Why do ovarian function, conception, and gestation continue in the presence of decreased metabolism?

Formerly, it was believed [4] that hypothyroidism of the mother would result in faulty fetal development, congenital defects, and a variety of thyroid disorders of the offspring. The investigations of Marine and Lenhart in 1909 [5] have been interpreted as meaning that the fetal thyroid is overstimulated during gestation and may suffer from exhaustion after birth. Recently, Peterson [6] found that the thyroid-stimulating hormone does not pass the placental barrier of guinea pigs. In the present study there was no evidence that the myxedema in a pregnant mother had any significant effect on the postnatal thyroid function of her children.

4. Davis,[1a] Herrgott, A.: Myxœdème: partuition et éclampsie, Ann. gynéc. et obst. **58**:1, 1902.

5. Marine, D., and Lenhart, C. H.: Effects of Administration or Withholding of Iodin-Containing Compounds in Normal, Colloid, or Actively Hyperplastic Thyroids of Dogs, Arch. Int. Med. **4**:253, 1909.

6. Peterson, R. R., and Young, W. C.: The Problem of Placental Permeability for Thyrotrophin, Propylthiouracil, and Thyroxine in the Guinea Pig, Endocrinology **50**:218, 1952.

These four living children were euthyroid, judging from clinical observation and results of laboratory studies.[7] The occurrence of several congenital defects in three of her four living children (one moron, one child with mongolism, a clawfoot deformity, a double canine tooth, and an undescended testis) suggests that this myxedematous mother provided an inadequate environment for normal growth and development of her fetuses. The malnutrition, retarded bone age, dental caries, and microcephaly may be attributed in part to faulty nutrition, poor home environment, and recurrent ear, nose, and throat infections.

There was no evidence, either historically or clinically, that the thyroid tissue of the growing fetus supplied thyroid hormone in quantities sufficient to increase the metabolism of this myxedematous mother. Mann [8] has shown that the serum-precipitable iodine (equivalent to our protein-bound iodine) rises considerably in normal pregnancy. It is a general belief that atrophy of a target organ, such as the thyroid, allows increased production of the trophic hormone which stimulates that organ. Thus, one might expect an increased level of thyroid-stimulating hormone in this myxedematous mother for two reasons: the pregnant state and the atrophy of the mother's thyroid. In spite of this presumed increased titer of thyroid-stimulating hormone in the mother, her newborn child had no evidence of goiter or hyperthyroidism, and, furthermore, at the age of 7 weeks thyroid function in this child had not decreased.

At present we cannot conjecture about the preservation of reproductive function in spite of myxedema, except to regard it as an unusual exception.

SUMMARY

A myxedematous mother first observed in her last month of pregnancy is described. She has been myxedematous for the past 15 years, during which time she conceived and delivered six children.

Four of these children were studied for evidence of thyroid dysfunction. They were found to be euthyroid.

No evidence was found to support the concept that the fetal thyroid function influenced maternal metabolism.

Numerous congenital and developmental defects in these children suggest that the myxedematous maternal state exerted a deleterious effect on the children.

A review of the literature reveals 16 cases of pregnancy occurring in myxedematous or cretinoid hypothyroidism.

7. Danowski, T. S.; Johnston, S. Y.; Price, W. C.; McKelvey, M.; Stevenson, S. S., and McCluskey, E. R.: Protein-Bound Iodine in Infants from Birth to One Year of Age, Pediatrics **7**:240, 1951. Quimby, E. H., and McCune, D. T.: Uptake of Radio-Active Iodine by Normal and Disordered Thyroid Gland in Children: Preliminary Report, Radiology **49**:201, 1947.

8. Mann, E. B.; Heineman, M.; Johnson, C. E.; Leary, D. C., and Peters, J. P.: The Precipitable Iodine of Serum in Normal Pregnancy and Its Relation to Abortions, J. Clin. Invest. **30**:137, 1951.

ADDISON'S DISEASE DUE TO CHRONIC DISSEMINATED COCCIDIOIDOMYCOSIS

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COCCIDIOIDOMYCOSIS in the disseminated form may involve any organ of the body with perhaps the exception of the epithelium of the gastrointestinal tract. Extensive involvement of the adrenal glands has been noted on many occasions at autopsy. In a series of 50 cases of disseminated coccidioidomycosis studied at autopsy by Forbes and Bestebreurtje, adrenal involvement was noted in 16.[1] It is a fact of historical interest that in the first case of coccidioidal granuloma described by Rixford in 1893 the adrenal glands were found at autopsy to be

> . . . the size of turkey's eggs, and on section were seen to contain great masses of necrotic tissue with nuclear degeneration resembling that in chronic tuberculosis, with empty shells of the organism; living organisms in the periphery.[2]

However, in view of the frequency of adrenal involvement in chronic disseminated coccidioidomycosis, it is a singular fact that Addison's disease due to destruction of the adrenal glands by coccidioidal granuloma has been described only once in the literature to date in a paper by Butt and Hoffman.[3] Their case is presented below.

It is intriguing that the clinical picture of Addison's disease due to disseminated coccidioidomycosis is such a rare entity. Why this is so is a matter of speculation, and we venture to suggest the following possibilities:

1. Early death may occur in disseminated coccidioidomycosis as a result of meningitis, extensive bronchopneumonia, or cardiac failure due to a coccidioidal myocarditis.

2. Complete destruction of the adrenal glands may occur rarely in the disease. It is estimated that less than 5% intact residual adrenal tissue must be present for the emergence of the typical clinical picture of Addison's disease.[4]

From the Medical Service of W. A. Winn, M.D., Medical Director of Tulare-Kings Counties Hospital, Springville, Calif.

1. Forbes, W. D., and Bestebreurtje, A. M.: Coccidioidomycosis: Study of 95 Cases of Disseminated Type with Special Reference to Pathogenesis of the Disease, Mil. Surgeon **99**:653-719 (Nov.) 1946.

2. Rixford, E.: Early History of Coccidioidal Granuloma in California, in Coccidioidal Granuloma, Special Bulletin No. 57, California Department of Health, 1931.

3. Butt, E. M., and Hoffman, A. M.: Healed or Arrested Pulmonary Coccidioidomycosis: Correlation of Coccidioidin Skin Tests with Autopsy Findings, Am. J. Path. **21**:485-505 (May) 1945.

4. Barker, N. W.: The Pathologic Anatomy in 28 Cases of Addison's Disease, Arch. Path. **8**:432-450 (Sept.) 1929.

Recent statistics reveal that in 50% of cases of Addison's disease adrenal destruction is due to primary idiopathic atrophy.[5] The majority of the remaining cases are due to bilateral caseous tuberculosis of the adrenal glands. With the decreasing incidence of tuberculosis, this cause is diminishing in frequency. Other rare causes are amyloid degeneration, metastasizing tumors of the lymphoma type, metastatic tumors from bronchogenic carcinoma,[6] hemorrhage due to either trauma or vascular disease, inflammatory changes associated with burns or sepsis, syphilis, adrenal tumors of the androgenic type causing replacement of the normal hormonal-producing cells of the adrenal cortex, and histoplasmosis. It is within the recent past that histoplasmosis of the adrenal gland causing Addison's disease has been reported.[7] From the point of view of the cases presented below, this is interesting, as both histoplasmosis and coccidioidomycosis are endemic diseases occurring rather frequently in certain areas of the United States. It seems likely, as Emerson states concerning histoplasmosis,[5] that fungous diseases may be a more frequent cause of adrenal disturbance than has been hitherto recognized.

REPORT OF CASES

CASE 1.—A 62-year-old American man, a railroad section foreman, was admitted to the hospital during March, 1942. He resided during the previous three years in Date, Ariz. His presenting complaint concerned swellings of the left knee and left wrist; these swellings contained discharging sinuses. He stated that his present illness commenced in 1940 with a soreness of the left big toe. The base of the left foot was incised by a local physician and "black blood" drained from the wound. The lesion healed, leaving no soreness. Two months later a swelling developed over the left inner ankle joint. This swelling broke, and a discharge was present for about a week. Over the next six months eight swellings appeared, one above the other along the inner aspect of the left leg. A swelling of the left knee was next noted; it came to a head and discharged "black blood." This lesion continued to drain until three months prior to his admission to the hospital, when the sinus closed. Over the three months prior to admission a swelling and a draining sinus appeared on the inner aspect of the left wrist.

The past history revealed that the patient was treated for pleurisy with effusion in 1921. A diagnosis of chronic fibroid tuberculosis was made at that time; however, tubercle bacilli were not isolated. In 1936 the patient experienced an attack of pain in the left shoulder area, which was considered to be a "subacromial bursitis." A chest x-ray at that time was interpreted as follows: "Pleural thickening is present over the apices and at the right base. No evidence of active disease is present." In a roentgenogram of the shoulder, no bone pathology was noted. A tonsillectomy was performed at that time.

On admission to the hospital the patient's temperature was 99 F., and the pulse rate was 84 per minute; the blood pressure was not recorded. The height was 5 ft. 9 in. (175 cm.) and his weight 130 lb. (59 kg.). He appeared fairly well developed but poorly nourished. The skin was noticed to be deeply pigmented in the exposed areas and less pigmented in the unexposed areas. Small crusted lesions were noted on the left side of the nasal septum. Examination of the chest revealed no dullness on percussion or adventitious sounds on auscultation. The heart size was thought to be within normal limits. On palpation of the abdomen, no enlargement of the abdominal viscera or tenderness was detected. A number of small oval pigmented skin lesions were present along the inner aspect of the left leg to the midthigh. The left knee joint was noted

5. Emerson, K., Jr.: Adrenal Disorders: Diagnosis, Pathology and Treatment, M. Clin. North America **35**:1283-1303 (Sept.) 1951.

6. Wallach, J. B., and Scharfman, W. B.: Addison's Disease Due to Metastatic Bronchogenic Carcinoma, J. A. M. A. **148**:729-731 (March 1) 1952.

7. O'Donnell, W. M.: Changing Pathogenesis of Addison's Disease with Special Reference to Amyloidosis, Arch. Int. Med. **86**:266-279 (Aug.) 1950.

to be enlarged. Two crusted lesions, probably representing the remnants of draining sinuses, were present on the inner aspect of the left patella. A similar crusted lesion was noted on the ulnar side of the left wrist, and below it were fluctuant lesions.

Laboratory Data.—A complete blood count on March 28, 1942 revealed 4,300,000 erythrocytes, 98% hemoglobin (Sahli), and 5,800 leucocytes per cubic millimeter. A differential leucocyte count showed 62% neutrophiles, 27% lymphocytes, 5% monocytes, 4% eosinophiles, and 2% basophiles. The Kahn test for syphilis was negative. On the next day a skin test for Sporotrichum and Coccidioides was reported as negative. On the same date a skin test with purified protein derivative (second strength) gave a strongly positive reaction. Roentgen studies performed on March 24 were interpreted as follows: "Left wrist, no bone pathology is visible. Chest, moderate bilateral hilar and bronchial scarring is seen. No areas of consolidation or cavitation are present. In comparison with films taken in 1936 no discernible changes are noted. There is no x-ray evidence of active disease at the present time."

Course in Hospital.—Five days following admission, a soft swelling occurred along the left patella, accompanied by a febrile reaction. This swelling was incised and drained and cultures

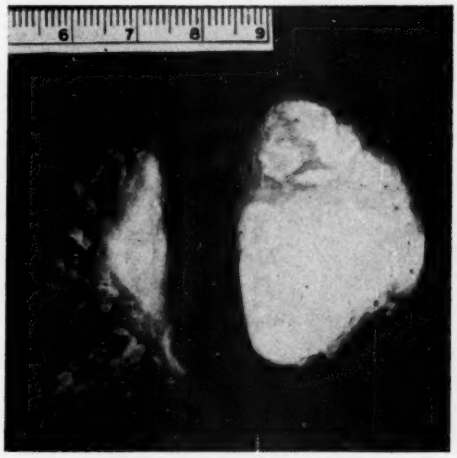


Fig. 1 (Case 1).—Right adrenal, showing destruction of parenchyma; weight 75 gm.

obtained from the wound surface. A biopsy specimen was obtained from the lesion of the left wrist at this time, and it also was cultured. These cultures were reported to be positive for Coccidioides immitis. On April 15 a skin test performed with coccidioidin obtained from another hospital was again reported as negative. On May 20 with Coccidioidin prepared from the patient's own organisms, positive reactions with dilutions of 1:100 and 1:10 were obtained. The patient was then treated with small doses of coccidioidin for a period of two months. During April and May, 1942, he complained of frequent bouts of nausea. During this period his course was gradually downhill, with daily elevations of temperature up to 102 F. At this time the blood pressure was first recorded and was found to be 60/40. A physician's note at that time remarked that owing to "the fact that the patient had gastric upsets, deeply pigmented skin and low blood pressure, adrenal cortical insufficiency may be present." Adrenal cortex extracts and 500 cc. of whole blood were administered. Despite treatment, the patient died on July 14, 1942. An autopsy was performed.

Autopsy Observations.—At autopsy a decided increase in brownish pigmentation was present over the face, neck, and nipple areas, with a less marked pigmentation present over the rest of the body. On the left leg a crusted lesion surrounded by deeply pigmented skin was noted about the lateral aspect of the patella.

Fig. 2 (Case 1).—Left adrenal; weight 90 gm.

Fig. 3 (Case 1).—Section of adrenal gland showing necrosis due to Coccidioides immitis with organisms present; × 65.

Grossly, the heart weighed 300 gm. The heart muscle was pale and flabby.

On gross examination adhesions were noted to be present between the base of the left lung and the diaphragm. The right pleural cavity was completely obliterated by fibrous adhesions. The parenchyma of the lungs was congested and edematous. The tracheobronchial nodes were markedly enlarged and partly calcified. In the upper lobe of the right lung a large oval area of calcification was present, surrounded by a fibrous tissue capsule. This lesion measured 3 cm. in diameter. The remaining portion of the lung was atelectatic, and moderately enlarged calcified lymph nodes were found in the peribronchial region at the hilus. Microscopically, the caseous lesion in the upper lobe of the right lung was found to consist of a central area of

Fig. 4 (Case 1).—Section of adrenal gland showing necrosis and spherule containing endospores; × 320.

hyalinized fibrous tissue bordered by irregular areas of necrosis in which remnants of lung tissue were seen. This entire area was surrounded by a thick fibrous capsule in which a few cellular tubercles were present. A large number of spherules of C. immitis were present, many of which showed endosporulation. In the centers of the necrotic areas the spherules showed varying degrees of alteration and calcification. Microscopically, a tracheobronchial lymph node showed replacement of the normal architecture by irregular areas of hyalinization containing heavy deposits of carbon pigment and remnants of spherules of C. immitis. Grossly, the adrenals appeared markedly enlarged. The right and left adrenals weighed 75 and 90 gm. respectively. No normal adrenal tissue was noted on section, it being completely replaced by yellowish and fibrous tissue. Microscopically, the parenchyma of the adrenals was replaced by large areas of

caseation necrosis separated by areas of granulation and fibrous tissue. Many large multinucleated giant cells were seen about the edges of the necrotic areas. Some of these contained spherules. Many spherules were found free in the edges of the necrotic areas. Endosporulation was present. No intact adrenal cortex tissue was found.

The final diagnoses were (1) arrested pulmonary coccidioidomycosis; (2) arrested coccidioidal granuloma of the tracheobronchial lymph nodes; (3) chronic suppurative coccidioidal granuloma involving the left knee and the left lower ulna; (4) Addison's disease due to coccidioidal involvement of the adrenals; (5) acute miliary coccidioidal granuloma, probably an extension of the involvement of the knee, wrist, and adrenals, and (6) chronic adhesive pleurisy.

A history of established coccidioidal disease of two years' duration was obtained in the above case. Signs and symptoms suggestive of Addison's disease were present ante mortem, and the diagnosis was suggested by an observer. The complete destruction of the adrenals by coccidioidal granulomas found at autopsy confirmed the diagnosis of Addison's disease. The primary pulmonary lesion was identified in this case. This lesion, as well as the lesion seen in the tracheobronchial lymph node appeared to be arrested. Of interest is the fact that the patient failed to react on skin testing with a standard preparation of coccidioidin. Such "anergy" is frequently seen in cases of disseminated coccidioidomycosis. However, the patient did react positively to the skin test performed with antigen prepared from his own organisms.

CASE 2.—C. N., a 44-year-old white American man, was admitted to Tulare-Kings Counties Hospital, Springville, Calif. on Nov. 1, 1951. His presenting complaints were extreme weakness with intractable nausea and vomiting. He stated that his present illness dated from an automobile accident sustained during October, 1950. At that time he incurred minor bruises to the chest which necessitated rest at home for about 10 days. He then returned to his occupation, which was that of operating a tractor, although he felt ill. In March, 1951, he noted the gradual development of increasing fatigue and marked weakness. He consulted his local physician, and he subsequently was referred to a chest physician because of some pulmonary pathology noted at that time. A diagnosis of "valley fever" was made, and he was advised to adhere to a regimen of strict bed rest. His physician has informed me that at that time the following diagnostic studies were carried out: Skin testing with purified protein derivative (second-strength) gave a 2+ reaction, and with coccidioidin (1:100) a 1+ reaction was obtained. Sputum examinations for tubercle bacilli were negative. Roentgen studies of the chest revealed a fine granular infiltrate present within both lung fields, with greater involvement of the left lung. A serological test for coccidioidal infection was done, and the conclusion was that it confirmed the coccidioidal origin of the lung lesion.

Despite strict bed rest the patient continued to feel very weak and tired. His appetite remained poor, and a progressive weight loss ensued. In September, 1951, a further serological test for coccidioidal infection was done, and the conclusion on this occasion was that "an exacerbation of his disseminated coccidioidal infection has occurred." During the following months marked weakness developed. Dizziness and blurring of vision were occasional symptoms. During October his anorexia became marked and intractable, with nausea and vomiting also being noted. The patient had not observed any color change of the skin, but his wife stated that his skin had become darker during the months of September and October. Because of progressive deterioration of his general condition, admission to Tulare-Kings Counties Hospital at Springville was advised. The family history was irrelevant.

The past history revealed that the patient had valley fever in 1940 and that he was hospitalized on two occasions in another institution because of this condition. A review was made of the clinical records of these admissions, and the following pertinent facts were elicited:

The initial hospitalization occurred in December, 1940. His presenting complaint concerned a swelling over the right shoulder blade. This had commenced about two years previously and had

intermittently discharged purulent material during the intervening period. One year after the appearance of the primary lesion, a second swelling occurred just beneath it. Slight fatigue and a 10-lb. (4.5-kg.) weight loss were the only constitutional symptoms elicited.

Physical examination at that time revealed two lesions draining purulent material over the right scapular area. A sinus track appeared to lead from the upper to the lower lesion. A wet smear of the pus was obtained, and oval bodies containing spores, morphologically resembling Coccidioides immitis, were noted. A culture of the pus revealed "mycelium of Coccidioides."

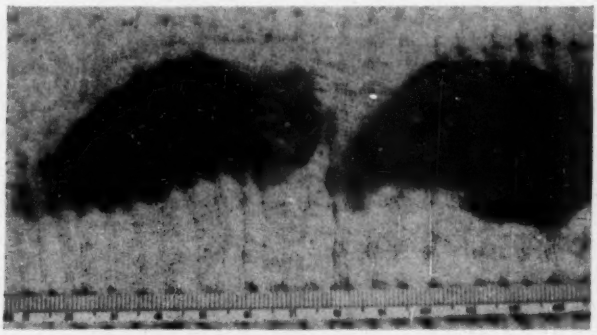


Fig. 5 (Case 2).—Gross appearance of the adrenal glands.

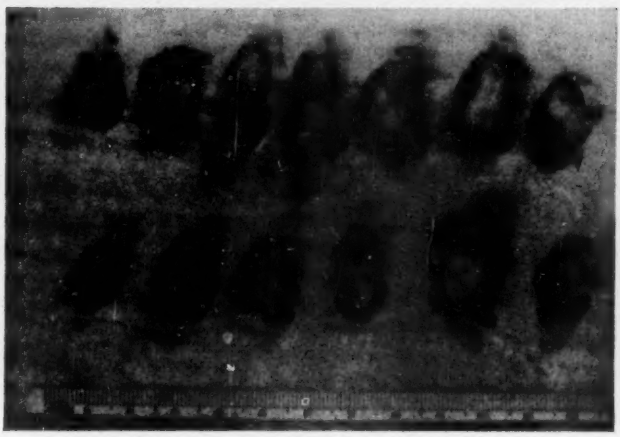


Fig. 6 (Case 2).—Appearance of the adrenal glands on gross section, showing necrosis.

A chest roentgenogram revealed "generalized haziness of the vascular markings which is compatible with the presence of minimal lobular infiltrate." The patient was discharged in January, 1941, and was admitted again to the same institution in May, 1941. His presenting complaint was a swelling over the upper end of the sternum which had commenced about 10 weeks previously. A purulent discharge had issued from the swelling on several occasions. Physical examination revealed a circular swelling 2 in. (5 cm.) in diameter over the upper sternum. It was fluctuant. Thick gray pus was aspirated from the lesion, and cultures revealed "mycelium of Coccidioides." The patient was discharged after an 11-day hospital stay unimproved. The blood pressure was not recorded during any of the above hospitalizations.

Results of Physical Examination on Last Hospital Admission.—The patient was a 44-year-old white man who appeared well developed but markedly malnourished. He was acutely ill and presented a Hippocratic facies. He was somewhat disoriented and unable to give a satisfactory history. The skin appeared markedly dehydrated. A peculiar brown mottling of the skin was present, with some cyanosis of the mucous membranes. Increased pigmentation of the face and discoloration of the buccal mucous membranes were also present. The rectal temperature on admission was 99 F. The pulse was rapid and weak at a rate of 120 per minute. The respiratory rate was 28 per minute. The systolic blood pressure was 60 mm. of mercury,

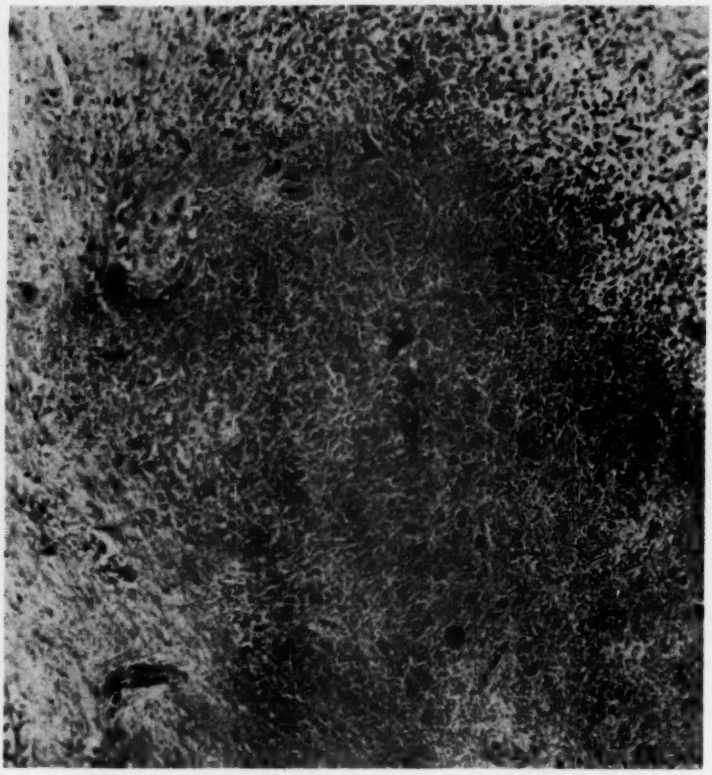


Fig. 7 (Case 2).—Section of adrenal gland showing necrosis and granulomatous process; × 100.

with an unobtainable diastolic pressure. Examination of the heart revealed faint heart sounds with a soft mitral systolic murmur. The breath sounds over both lung fields appeared diminished in intensity.

Laboratory Data.—A complete blood count revealed 5,150,000 erythrocytes per cubic millimeter, 98% hemoglobin per cubic millimeter (Sahli), 15.3 gm. of hemoglobin per 100 cc., and 13,500 leucocytes per cubic millimeter. A differential leucocyte count showed 54% neutrophiles, of which 50% were segmented cells, 31% lymphocytes, 5% monocytes, and 10% eosinophiles. A corrected erythrocyte sedimentation rate was 24 mm. at one hour, Wintrobe method. The volume of packed cells was 50%. A urinalysis on Nov. 2, 1951, revealed a clear yellow color, with a specific gravity of 1.018 and an acid reaction. A trace of albumin was present, and a

2+ sugar reaction was obtained. Microscopic examination showed frequent hyaline casts, and occasional pus cells were detected. A trace of albumin was present, and a 2+ reaction for sugar was obtained. It should be stated that the above urine was obtained after the patient had received dextrose and saline solutions parenterally. Fasting blood sugar on the same date was 129 mg. per 100 cc. Serum chlorides were 260 mg. per 100 cc. as sodium chloride (normal range in our laboratory, 580 to 620 mg. per 100 cc). Nonprotein nitrogen was 58.5 mg. per 100 cc. The Kahn and Kline reactions were negative. Roentgen studies performed on Nov. 6 were interpreted as follows:

"In this posteroanterior view of the chest an infiltrative process is seen to occupy most of both lung fields, with greater involvement in the upper half. There is a finely granular mottled infiltrate present, and in the left apex there is some evidence of annular shadows, possibly representing underlying bronchiectatic change. Prominent calcified lymph nodes exist in the left hilus. An abdominal plate discloses normal muscle shadows. Calcification in the region of the adrenal glands is not noted."

Course in the Hospital.—A diagnosis of acute adrenal insufficiency was made, and therapy was commenced immediately. Hypertonic dextrose and saline solutions, aqueous adrenal cortex extract, cortisone, and antibiotics were administered by the parenteral route. During the following 12 hours, the patient appeared clinically improved and a rise in blood pressure to 75/40 was obtained. The patient's nausea and vomiting became less marked. On Nov. 2 desoxycorticosterone acetate and sodium chloride enseals® (timed disintegrating tablets) were administered, together with further hypertonic dextrose and saline solution, added aqueous adrenal cortex extract, and cortisone. A further rise in blood pressure ensued, and the patient ceased to vomit and was able to take a light diet. On Nov. 3 a maintenance dosage of cortisone, 12.5 mg. daily, desoxycorticosterone acetate, and sodium chloride was established, and over the next five days the patient's condition continued to improve. His blood pressure on Nov. 4 was 110/75 and remained at that level. His clinical condition appeared much improved, and he was afebrile. His blood chloride level on Nov. 5 had risen to 285 mg. per 100 cc. The urinalysis on that date gave normal results. On the night of Nov. 8 the patient suddenly began to perspire profusely, his pulse became irregular and weak, and he suddenly died. An autopsy was performed.

Autopsy Observations.—At autopsy, a faint brown discoloration of the skin of the face was noted. There were scattered, light tan, pigmented zones over other portions of the body.

Grossly, the heart revealed moderate coronary sclerosis. The ventricular chambers were dilated, and the myocardium was soft and mottled. Microscopically, there were numerous areas of interstitial edema within which were occasional small numbers of round cells, rare polymorphonuclear leucocytes, and occasional Anitschkow myocytes.

Grossly, numerous fibrous nodular zones were present within both upper lobes of the lungs. Miliary nodules up to approximately 2 mm. in diameter, with bright yellow centers and gray-white peripheries, were also scattered throughout the entire right lung and the left upper lobe. The hilar lymph nodes were moderately enlarged and also contained gray-white or yellow miliary granulomatous areas. A diffuse purulent bronchiectasis of the right lower lobe was present.

The adrenal glands together weighed 20 gm. They were firmly adherent to surrounding fat tissue. Their normal architecture was completely replaced by numerous round, bright yellow, soft zones, some of which were surrounded by gray capsules.

Microscopically, there were numerous granulomas, almost entirely replacing both adrenal glands, throughout both lungs and within grossly involved lymph nodes. Similar granulomas were present within the spleen. All were old and consisted of extensive areas of fibrosis, some surrounding areas of caseation-like necrosis. There were varying numbers of epithelioid cells, round cells, and mononuclear cells. Occasional multinucleated giant cells were also present. In many areas, the granulomas were replaced by dense, eosinophilic, hyalinized connective tissue. Careful search of involved tissues failed to reveal acid-fast organisms by means of Ziehl-Neelsen stain. With a Hotchkiss-McManus stain, several ill-defined red structures were noted within a zone of caseation within a lung. These were approximately 10 to 20 μ in diameter. Within the adrenal glands, a single, small spherule was found, approximately 5 μ in diameter. This was located within a multinucleated giant cell.

In a section of the brain, there were several multinucleated giant cells, round cells, and occasional epithelioid cells within the meninges. However, a well-formed granuloma was not encountered. No spherules could be demonstrated.

The kidneys were moderately involved by arteriolonephrosclerosis, and there was a small area of renal papillary necrosis.

The final diagnoses were (1) "disseminated coccidioidal granulomas, with involvement of lungs and adrenal glands, periaortic and hilar lymph nodes, and meninges"; (2) "extensive destruction of adrenal tissue by coccidioidal granulomas," and (3) "subacute myocarditis."

COMMENT

It is our opinion that the case presented above is one of Addison's disease. We predicate this on the basis of the typical clinical history, the results of physical examination and pertinent laboratory studies, the response to therapy, and the observations on autopsy. We base our conclusion of destruction of the adrenal glands by coccidioidal granuloma on the 10-year history of coccidioidal disease, positive skin reaction to coccidioidin, the positive serial serological tests for coccidioidal infection, and the histologic reaction observed at autopsy. We feel that an excerpt from the pathologist's autopsy report should be appended:

The spherules certainly were not diagnostic of Coccidioides immitis. However, these atypical structures, in addition to the history and the strongly positive serologic reactions, suggested that the anatomic findings were the end-result of a long-standing disseminated coccidioidal infection.

SUMMARY

Two cases of Addison's disease due to extensive destruction of the adrenal glands by disseminated coccidioidal disease are presented. Addison's disease due to adrenal destruction by disseminated coccidioidomycosis has not been previously reported. Fungous disease may be a more frequent cause of adrenal pathology than has hitherto been suspected.

Dr. E. M. Butt, Department of Pathology, University of Southern California and Los Angeles County General Hospital, supplied the protocol and autopsy report of Case 1. Dr. Charles E. Smith, University of California, Berkeley, Calif., made available the results of the serological tests. Dr. George Amromin, Exeter, Calif., furnished the autopsy report on Case 2. Mr. Verne Long, laboratory technician, gave technical assistance.

News and Comment

ANNOUNCEMENTS

Western Society for Clinical Research.—The sixth annual meeting of the Western Society for Clinical Research will be held at Carmel, Calif., Jan. 30-31, 1953.

Fellowships in Physical Medicine and Rehabilitation.—The National Foundation for Infantile Paralysis announces the availability of a limited number of postdoctoral clinical fellowships in physical medicine and rehabilitation to candidates who wish to become eligible for certification in that field. Fellowships will cover a period of one to three years at training centers which have been approved for residencies in physical medicine and rehabilitation. Stipends to fellows are based on the individual need of each applicant. Eligibility requirements include United States citizenship, graduation from an approved school of medicine, completion of at least a one-year internship in an approved hospital, and a license to practice medicine in at least one state. The age limit is 40.

The National Foundation is also making available a limited number of short-term fellowships to physicians who wish to become better acquainted with physical medicine and rehabilitation as it relates to their particular specialties. Such training is being offered to physicians who, in addition to meeting the other requirements, have completed a minimum of a one-year residency in orthopedics, pediatrics, neurology, or internal medicine. These fellowships will cover a period of training of three months to one year at centers which place special emphasis on physical medicine in relation to the applicant's specialty.

Complete information concerning qualifications and applications for both types of fellowships may be obtained from the Division of Professional Education, the National Foundation for Infantile Paralysis, 120 Broadway, New York 5.

Course on Recent Advances in Diagnosis.—The University of Minnesota will present a continuation course in Recent Advances in Diagnosis for Internists at the Center for Continuation Study on Feb. 16 to 18, 1953. Although intended primarily for specialists in internal medicine, the program will be of interest to many pediatricians and general physicians. This course will provide information concerning techniques which have ben introduced or developed within the past 5 to 10 years which have increased our knowledge of basic physiology and which are becoming or give promise of becoming standard diagnostic procedures. Recent developments in the fields of cardiology, respiratory disease, renal disease, hematology, gastroenterology, and endocrinology will be emphasized.

Under the direction of Dr. C. J. Watson, professor and director of the department of medicine, an outstanding guest faculty has been assembled: Dr. Carl V. Moore, professor, department of medicine, Washington University School of Medicine, St. Louis; Dr. Thomas E. Machella, assistant professor, department of medicine, and associate in physiology, University of Pennsylvania School of Medicine, and chief of gastrointestinal clinic, Hospital of the University of Pennsylvania, Philadelphia; Dr. Robert P. Grant, U. S. Public Health Service Hospital, Baltimore; and Dr. William W. Engstrom, associate professor, department of medicine, Marquette University School of Medicine, and director, metabolism section, Milwaukee County Hospital. The remainder of the faculty will include clinical and full-time members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

Lodging and meal accommodations are available at the Center for Continuation Study.

Postgraduate Course in Diabetes and Basic Metabolic Problems.—The first postgraduate course in diabetes and basic metabolic problems to be conducted by the American Diabetes Association will be offered under the direction of Charles H. Best, C.B.E., M.D., F.R.S., director of the Banting and Best department of medical research of the University of Toronto, on Jan. 19, 20, and 21, 1953, at the University of Toronto, Canada.

Developed by the Association's Committee on Postgraduate Education, under the chairmanship of Edward L. Bortz, M.D., the course will have as its clinical director, Ray F. Farquharson, M.B., professor of medicine of the University of Toronto, and Andrew L. Chute, M.D., professor of pediatrics of the University of Toronto, will act as associate clinical director.

Over 30 lectures and round-table discussions have been planned as well as a social evening. The course is open to nonmember physicians as well as members of the American Diabetes Association, but the number of registrants will be limited to 100. Fees are $20 for members and $40 for nonmembers. Details of the three-day program and registration and hotel information may be obtained from J. Richard Connelly, Executive Director, American Diabetes Association, 11 West 42nd Street, New York 36, N. Y.

To date the following program has been arranged:

Manifestations of Diabetes: Clinical, Howard F. Root, M.D.; Pathological, J. D. Hamilton, M.D.; Clinical Features of Diabetic Acidosis and Coma, E. Perry McCullagh, M.D.; Electrolyte Metabolism in Diabetic Acidosis, Randall G. Sprague, M.D.; Treatment of Coma, Herbert Pollack, M.D. Round-table discussion.

Experimental Diabetes, Francis D. W. Lukens, M.D.; The Adrenals in Relation to Diabetes, Jerome W. Conn, M.D.; The Action of Insulin, Charles H. Best, M.D.; Cholesterol, Henry T. Ricketts, M.D. Round-table discussion.

Complications of Diabetes: Cardiovascular Complications, Howard F. Root, M.D.; Ocular Complications, John C. McCulloch, M.D.; Neurological Complications, H. J. M. Barnett, M.D.; Errors in Treatment, Henry B. Mulholland, M.D.; Infectious Complications, Francis D. W. Lukens, M.D. Round-table discussion.

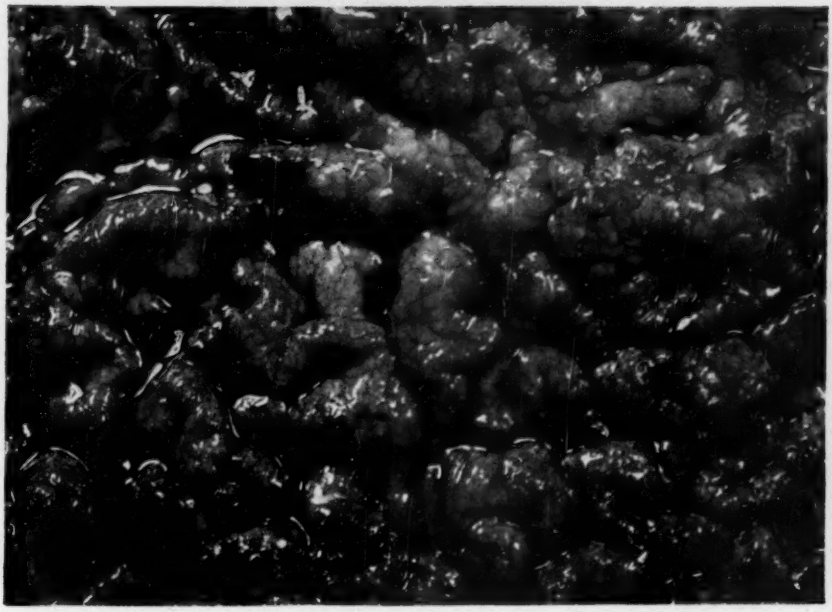
Management of Diabetes in Infancy, Robert L. Jackson, M.D.; Management of Diabetes in Childhood, Andrew L. Chute, M.D.; The Prognosis in Juvenile Diabetes, W. T. W. Clarke, M.D.; Acidosis in Children, George M. Guest, M.D.; Problems in Insulin Therapy, Including Allergy and Resistance, Arthur R. Colwell, M.D.; Insurance for Diabetics, R. C. Montgomery, M.B.

Management of Diabetes: Diabetes Control, Edward L. Bortz, M.D.; Dietary Instruction, Deaconess Maude Behrman; Properties of the Different Insulins, A. M. Fisher, Ph.D.; Clinical Use of Insulin, Arthur R. Colwell, M.D.; Surgical Problems in Diabetes, Gordon Murray, M.B. Round-table discussion.

Hyperinsulinism, W. R. Campbell, M.D.; Hypoglycemia, Neurological Manifestations, J. C. Richardson, M.D.; Factors Affecting the Islands of Langerhans, R. E. Haist, M.D.; Insulin Content of the Pancreas, G. A. Wrenshall, Ph.D. Visit to the laboratories of the department of medical research, conducted by Charles H. Best, M.D.

CORRECTION

In the article by Thomas N. James, M.D., on "Enterococcal Endocarditis," published in the November issue, page 646, the following footnote was omitted "From the Cardiology Division of the Henry Ford Hospital."



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*Asher, L. M.: The Use of Banthine in the Treatment of Digestive Disturbances, California Med. *76*: 137 (March) 1952

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: N.Y. State J. Med. 52:2012 (Aug. 15) 1952.

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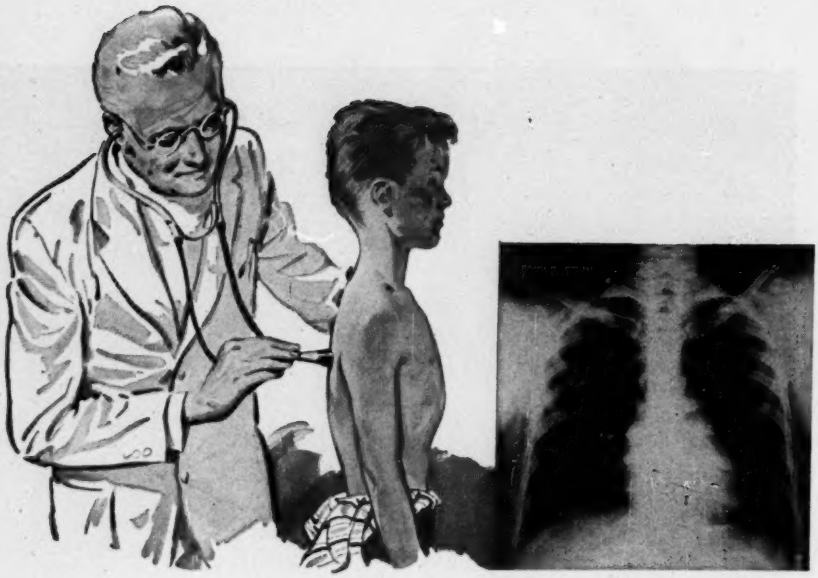

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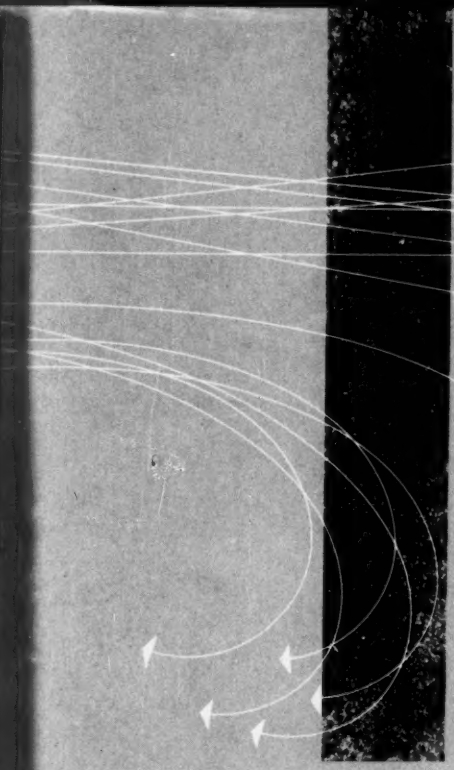

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1. Thorn, G. W., and Tyler, F. H.: *Med. Clin. North America*, 31:1081, Sept. 1947.

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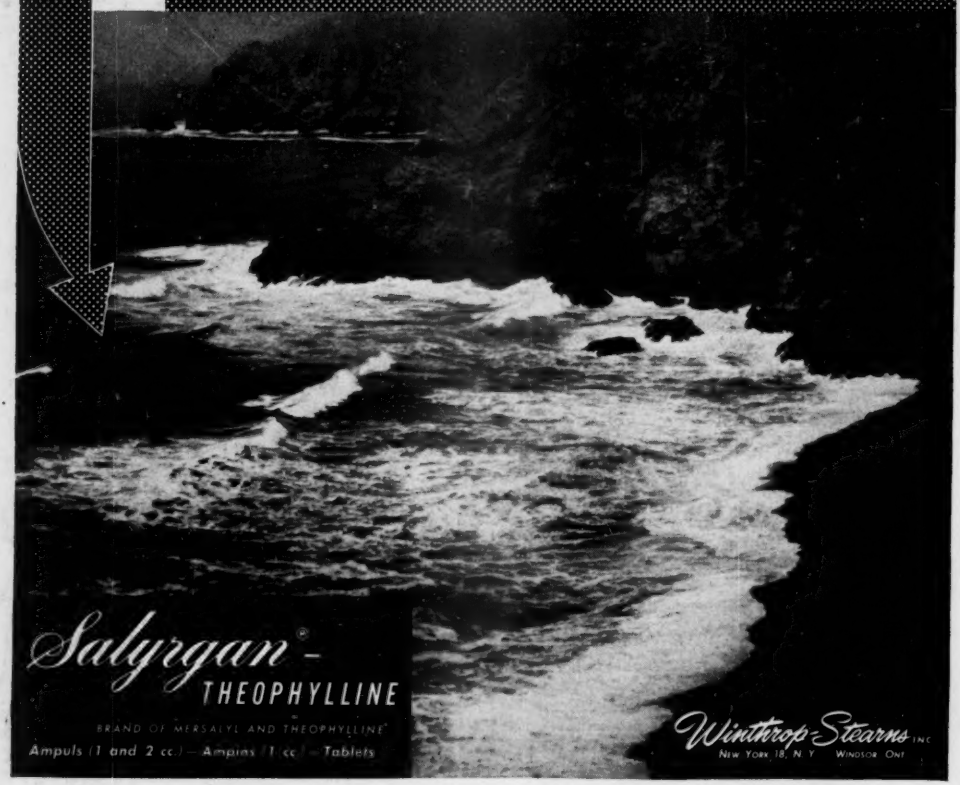

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